THE BLOOD VESSELS
OF THE HUMAN SKIN
AND THEIR RESPONSES

BY

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PREFACE.

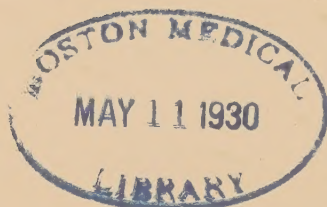THE present monograph describes a series of investigations begun eleven years ago and since continued from time to time ; the work has been carried out on behalf of the Medical Research Council. The book, as its title indicates, deals with the cutaneous circulation, being especially intended to show how the vessels of the skin change in response to local conditions. It is compiled in part from articles already published. The first of this series of articles was that written in collaboration with Drs. T. F. Cotton and D. L. Rapport in 1916 ; later articles have been published in collaboration with Dr. Ronald Grant, Dr. W. S. Love, Dr. Y. Zotterman, Miss I. Harmer and Dr. H. M. Marvin.

An initial reason for considering the collection of these and other observations under one cover was that by so doing I should be able to present them in a more connected and readable form, than was possible in original papers published often at considerable intervals. But the chief motive, which eventually led me to write this book, was a different one, namely, a desire to stimulate a wider study and teaching of human physiology ; for knowledge relating to the healthy man forms the most manifest and abiding bond between Physiology and Medicine.

It is common ground that main aims of physiological teaching to medical students are to imbue them with powers of accurate

observation and with the principles governing sound inference and conclusion, while rendering them familiar with the functions of the body. Theoretically these aims may be fulfilled by following through a natural and orderly sequence of phenomena, of which animal physiology now presents many almost perfect illustrations. To choose an equally unbroken series from human physiology is not often possible, whence, presumably, human physiology tends to become subsidiary. Thus shaped, the physiological syllabus is apt to overlook two important and relevant considerations.

Firstly, that it is vital to successful teaching to awaken and secure interest and keen attention ; and in this the illustration from human physiology is possessed of well recognised and I think unrivalled force. Something, if not much, may be sacrificed to this object.

Secondly, and no less important, it is to be remembered that the greatest number of those who pass through the physiological theatre and laboratory go on to a continuous and exclusive study of mankind. A very large part of the physiological knowledge that they acquire is to find in the hospital and in practice no application, immediate or remote ; for this reason much of it rusts and is lost. Moreover, because the methods of the ward are necessarily less direct, are necessarily cruder than the methods of the laboratory, the transition from the more exact to the less exact tends to destroy reliance on physiology as a working basis, and to weaken confidence that Medicine can be prosecuted successfully as a Science. If the

student comes, as he so often does to the wards, with little knowledge of the many phenomena manifested by normal men, and largely unversed in methods alone suited to human investigation, he will be in a position neither to discriminate between the normal and the abnormal, nor to use his new measures with due regard to the magnitude of the errors that these will include.

It is to these defects in the upbringing of medical men that very many current mistakes in the interpretation of symptoms and signs of disease are due ; it is these same defects that permit his accepting, as exact, methods fraught with very material error. As a matter of fact the study of human physiology has progressed sufficiently in many directions to enable the physiological teacher to select consecutive observations and experiments that illustrate legitimate processes of reasoning both deductive and inductive, and it is submitted that such examples could be made to form an invaluable part of a medical student's training, since, while knowledge of the phenomena witnessed would be directly and continuously applicable in his life's work, the illustration, the conclusions derived from it, and the method by which these conclusions are reached would on that account impress him more lastingly. In writing the following chapters, the ideas here expressed have been held in view, for reactions of the normal skin seem to me to present many opportunities to the physiological teacher, not only for imparting serviceable knowledge but also for their educative values in the arrangement and proper use of evidences,

and especially in the strict control of observations that, like so many observations relied upon by practitioners in their professional work, are essentially subjective.

In the following chapters I am careful to refer to the source of my information. Where no such source is quoted, I refer to facts long recognised as true or to observations I have personally made. So far as observations upon the human skin are concerned, there are but few instances in which I have cited the authority of another worker, without myself verifying the observations.

Professor T. R. Elliott, my friend and colleague of many years, generously consented to read the chapters in their manuscript stage. I gratefully acknowledge his helpful criticisms. To Dr. Ronald Grant and to Dr. H. M. Marvin, of New Haven, who have worked with me in the same field, I am greatly indebted for their very careful reading and criticism of the proof sheets.

THOMAS LEWIS,

December the 4th, 1926.

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CHAPTER I.

INTRODUCTORY OBSERVATIONS.

Anatomical notes.

THE arrangement of the cutaneous vessels has been fully described and illustrated by Spalteholz (231). His account published in 1893 is here closely followed.*

According to this authority the number, and often size, of vessels running to the skin varies in different situations, the number being greater to skin, such as that of the palms of the hands and soles of the feet and the gluteal region, that often experiences external pressure. All branches of these arteries anastomose very freely with each other and with neighbouring vessels, and thus form in the deepest layer of the cutis, where it joins the fat, a characteristic *cutaneous arterial network* (Fig. 2, page 5). The mesh of this network is smaller in the more vascular regions named above ; from it *arched* and branching vessels proceed outwards and anastomosing form a second *subpapillary arterial network* near the junction of the middle and outer thirds of the cutis. The meshes of this network vary in size ; in the sole of the foot the areas enclosed average 0·3 of a square millimetre, in the less vascular skin of the calf and gluteal regions they are larger and approach 1 and 1·5 square millimetres.

Numerous small branches arise from the subpapillary network and run as *terminal arterioles* to the superficial layers of the skin. Most of these turn and course for a short distance parallel to the surface of the skin, following in the palm of the hand and sole of the foot the direction of the papillary ridges beneath which they run. They send their twigs to the arterial limbs of the capillary loops, lying in the papillæ. The skin surface which the branches of the subpapillary plexus supply is in the average 0·16 of a square millimetre.

In his latest account Spalteholz (231a) describes the arteries of the cutaneous arterial network as possessing a thick muscular coat, which diminishes relatively abruptly about the middle of the corium, where the vessels are

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* With Dr. Grant I have injected and examined many specimens of human skin, for my own satisfaction and not in the expectation of finding other than Spalteholz has found, for his skill in this field of work is unrivalled. It would not be exact to state that our personal observations have confirmed his, but truer to state that in our less perfect preparations we can see clearly the broad arrangement of vessels that he describes.

clothed by a single layer of muscle cells. Traced farther this layer becomes imperfect, though muscle elements are still discovered on the vessels of the subpapillary arteriolar plexus and even on the terminal arterioles. In his earlier account (*231*) the muscular coat is described as lost before the sub-papillary plexus is reached ; with this earlier statement Vimtrup's description (*256*) agrees, except that he believes the muscular coat to be replaced by scattered, obliquely placed, and contractile "Rouget's" cells (see page 35).

The venous blood returning from the papillæ passes through several networks. The first lies immediately beneath the bases of the papillæ and receives blood from the venous limbs of the capillary loops, and from minute collecting venules formed by the union of several such capillaries ; in the sole of the foot the main lines of this plexus are straight and correspond to the skin ridges, but they, unlike the terminal arterioles with which they run, anastomose by short venules running at right angles. Almost immediately beneath this is a second venous network, the two intercommunicating freely by short venules ; they are often spoken of together as forming the *sub-papillary venous plexus* ; it lies a little superficial to the correspondingly named arterial network. The blood flows deeper by numerous tributaries to third and fourth venous networks, the former lying immediately deep to the subpapillary arterial plexus, the latter at the level of the cutaneous plexus of arteries, where cutis and subcutis join.

The superficial venous plexuses are formed of endothelium only, according to Spalteholz (*231a*) ; as the venules are traced more deeply their walls present scattered muscle cells, which become more numerous as the last venous network is reached, and there form an imperfect sheath to the vessels. Valves and full muscular coat first appear in the subcuticular veins.

Spalteholz believes that there are no communications between the arterial and venous sides of this vascular system, except superficially in the papillæ ; thus in the strictly architectural sense the papillary loops would alone constitute capillaries, and all blood passing to the skin would pass through these loops. Strictly speaking, however, it is incorrect to regard the fully formed and quite superficial capillary loops as the sole inter-communications. The junctions between terminal arterioles (or the branches into which these divide in supplying two or more capillary loops) and the collecting venules are sometimes shorter and take a deeper and straighter course in the skin (*160, page 176*). Two short communicating loops are shown between the arterial and venous limbs of the main twisted loops to the left in Fig. 6, page 13.* Such intercommunications may be even more direct and may end, not in the venous stem of the main loop, but in a collecting venule, or even in a venule belonging to the subpapillary plexus

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* Certain deeper and direct communications have been described between arterioles and venules in the bed of the nail and pulp of the fingers and toes by Hoyer (*121*) and others, and are recognised by Spalteholz (*231a*). These communications are further dealt with in Chapter XX. Heimberger confuses with these the superficial capillary anastomoses that he describes. The deep communications are true arteriovenous anastomoses, the arterioles concerned being heavily coated with muscle.

as Heimberger (*112a*) has stated. Where the vessels are arranged upon this or upon an even less simple plan, or where the terminal arteriole breaks up abruptly into several branches as shown in Fig. 7, page 13, we are obviously entitled to regard the whole arrangement as a capillary meshwork. Although the simple plan may be perhaps the usual one, and would permit of our confining the term capillary strictly to the loop, the less simple and less usual arrangements render such a definition precarious.

The broad arrangement of the vessels may be followed in the accompanying diagram (Fig. 2), which is modified from that published by Spalteholz himself. It represents the manner in which the vessels are disposed in the sole of the foot or palm of the hand, but the same general plan may be recognised in the skin of other parts of the body.

It is agreed that the arterioles strongly coated with muscle lie deep to the subpapillary arteriolar plexus. The vessels of this plexus and the terminal arterioles may possess a slight covering of these muscular elements. From a structural standpoint, therefore, we may speak of the arterioles, traced as far peripherally as the arched arterioles, as strongly equipped with muscle ; from here onwards they are at the most weakly equipped. The capillaries, collecting venules, and venules of the subpapillary plexus are by consent simple endothelial tubes ; this group, and less decidedly the weakly equipped arterioles with a greater or lesser portion of the deeper venules, may be regarded as forming from a physiological standpoint a complex meshwork of endothelial vessels, capable of nourishing the surrounding tissues.

Structurally the main differentiation comes on the arterial side in the region of the arched arterioles ; there is evidence, to be recorded later, that in this region a physiological subdivision may also be made.

It may assist if, before closing this anatomical description, I call attention to the vessels with which we shall be concerned chiefly in this book and to certain terms that for convenience I propose to use. In some instances it will be possible to specify the exact order of vessel that is under examination or that is concerned in a reaction. This is so in the case of those superficial vessels that can be rendered visible in the living skin ; these are, as we shall see, the *terminal arterioles*, the *capillaries*, the *collecting venules* and the *subpapillary venous plexus*. To these I shall sometimes refer individually in precise terms ; at other times, and to shorten description, I shall call the vessels here scheduled, the **minute vessels.** It is true that the vessels of the subpapillary arteriolar plexus are also minute ; but this plexus is not open to investigation and I shall have little to say or infer about it. As we go back along the arterial tree, we come soon to the *arched arterioles*, arterioles of more considerable size, but the smallest of those possessing a considerable muscular coat. Of these I shall sometimes speak specifically. At other times I shall use the term strongly muscled or **strong arterioles** ; in so doing I shall be referring to arterioles of the skin of all sizes down to the arched arterioles without further differentiation ; it is convenient to

Fig. 1. The bed of a finger nail in a healthy subject of 44 years, showing the capillary loops and the summits of the skin papillæ, from the undisturbed living skin. For this and similar sketches the size of the structures is accurately indicated by the 1/10 mm. scale.

Fig. 2. ($\times$ 12 approx.).* A diagram of the skin and its vessels, showing the arrangement of the arterial and venous plexuses at various levels. (After Spalteholz.)

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* The magnification given here and in subsequent figures is linear and expresses the relative sizes of the object and of its reproduction.

Fig. 1.
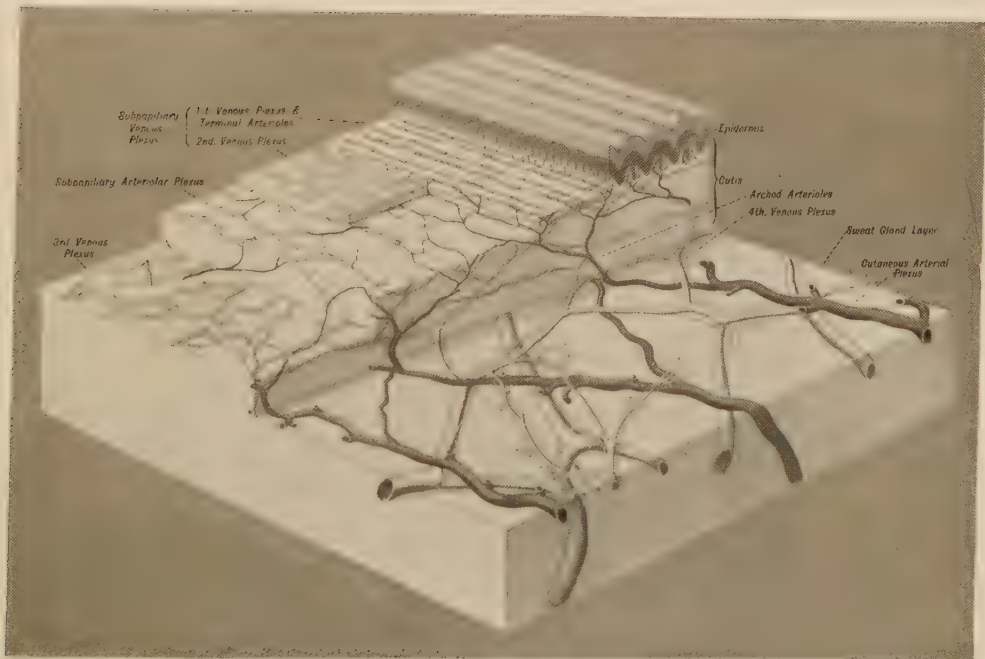
Fig. 2.

possess a term that may be taken in this sense and one that does not comprise arterioles belonging to the minute vessel class. The venules beyond the subpapillary plexus I shall refer to as the **deep veins.** To render this classification unmistakable I place the terms now defined against those named by Spalteholz.

Main cutaneous arteries
Cutaneous arterial network } **Strong arterioles.**
Arched arterioles

Branches of the last
Subpapillary arterial network

Terminal arterioles
Capillaries
Collecting venules } **Minute vessels.**
1st venous plexus } **Subpapillary**
2nd venous plexus } **venous plexus.**

Communicating veins
3rd venous plexus
Communicating veins } **Deep veins.**
4th venous plexus
Main cutaneous veins

Methods of studying blood supply to the skin.

In studying the physiology of the cutaneous circulation in man several methods are available. One is to examine and watch the vessels of the skin microscopically. A second is to study skin temperature and its change in response to various influences. A third, and by itself perhaps the most valuable, is the study of skin colour and its changes ; these as we shall see are various ; the skin may pale or it may redden, and the reddening may be of one or more types according to the order of vessel involved.

Each of the three methods has its distinct value ; each has limitations, but these in large part disappear when the methods are used, as they should be used, not separately but in judicious combination.

Visible vessels in the living skin.—In 1912, Lombard (*179*), in studying capillary blood pressure found that the superficial vessels are rendered clearly visible by illuminating the skin and placing a highly refractile oil upon it. The method has undergone development, in the hands of Weiss (*261, 262*), Müller (*197*), and others, and has been used widely for observing changes in these vessels. It is simple, but its employment requires care and the results that it yields are limited. The illumination should be brilliant and is commonly derived from an arc or high power filament lamp, the light being concentrated by lenses. The light must be filtered ; for this purpose suitable blue screens are employed, which cut out the heat rays from the one end and

Fig. 3. The unmolested living skin of the nail bed in a lad of 15 years, showing capillary loops and part of the venous plexus.

Fig. 4. The unmolested and living skin of the back of the hand, in a lad of 19 years ; the tops of the capillary loops and, dimly, small portions of the venous plexus are shown. A furrow crosses the field diagonally.

Fig. 3.

Fig. 4.

the ultraviolet rays from the other end of the spectrum. The filter increases the clarity with which the vessels are seen, though its primary purpose is to prevent reaction of the skin vessels to heat. Any low power microscope suffices, but for work on many parts of the skin it is convenient to mount the microscope upon a long movable arm under nice control and adjustment. A binocular arrangement enables us to determine more readily the relative depths at which various vessels lie.*

In treating the skin beforehand its surface may be dehydrated with alcohol, cedar wood or paraffin oil being subsequently placed upon it. Rubbing the skin, or the application of any oil that irritates the skin during the period of observation, is not permissible if the natural circulation is under study. When it is desired to study a full flow in the vessels, or to obtain a clearer and deeper view of the vessels as a whole, the horny layer may be removed by preliminary blistering (Figs. 5 to 7, page 13).

Using these methods, it is almost always possible to obtain a clear view of the capillary loops and dimly to see the subpapillary plexuses. The capillary loops lie usually in the length of the papillæ and therefore in most instances at right angles to the skin surface (Fig. 4, page 9), there being as a rule a single loop to each papilla. In the fingers, immediately above the bed of the nail, the skin is adherent to the nail and the capillary loops are drawn into the plane of the nail itself (Fig. 1, page 5, and Fig. 3, page 9). Here usually, and in other parts less usually, the flow of blood can be detected and its rate estimated. Usually after blistering, exceptionally without this interference, the collecting venules and subpapillary venous plexus are seen quite sharply (Fig. 5, page 13) and the blood flow may be discerned in these also ; not infrequently the terminal arterioles and their subdivisions are also distinguishable (Figs. 5 to 7, page 13). The method has several limitations ; a very small area of skin is under observation at a given moment ; the method reveals the events in the most superficial vessels only and even in these, with the exception of the finger nail bed and areas in which the circulation has been disturbed by preliminary treatment of the skin, often no more than an indistinct view is obtained.

Skin temperature.—To measure skin temperature and its changes, thermo-electric couples are employed (*160*). The general arrangement of the apparatus is illustrated in Fig. 8. The circuit consists of two junctions of suitable metals such as copper and constantan, a resistance box, a simple key and a sensitive mirror galvanometer, arranged in series. One junction is immersed in water in a thermos flask and is there maintained at a constant temperature, the other or testing junction is applied to the skin. A difference in the temperature of the two junctions is signalled by a deflection of the galvanometer, and its amount is readily determined by subsequently calibrating the instrument, placing the testing junction in water at suitable and known temperatures. The excursion of the galvanometer corresponding

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*A very serviceable instrument is Greenough's binocular microscope as supplied by Zeiss.

Fig. 5. Skin of the forearm in a young and healthy man. The horny layer
has been removed by blistering. Terminal arterioles (*aa*) capillary
loops, and venules, down to and including the subpapillary venous
plexus, are shown.

Fig. 6. Skin of the nail bed in a living subject. The horny layer has been
removed by blistering. The terminal arterioles break into branches
that supply twisted capillary loops, and the blood returns through
collecting venules to the meshwork of the subpapillary venous plexus.

Fig. 7. Skin of the nail bed of a healthy boy. The horny layer has been
removed by blistering. A terminal arteriole (*a*) breaks into three
branches, one of which subdivides ; four capillary loops are thus
supplied, and pour their contents into a single efferent venule.
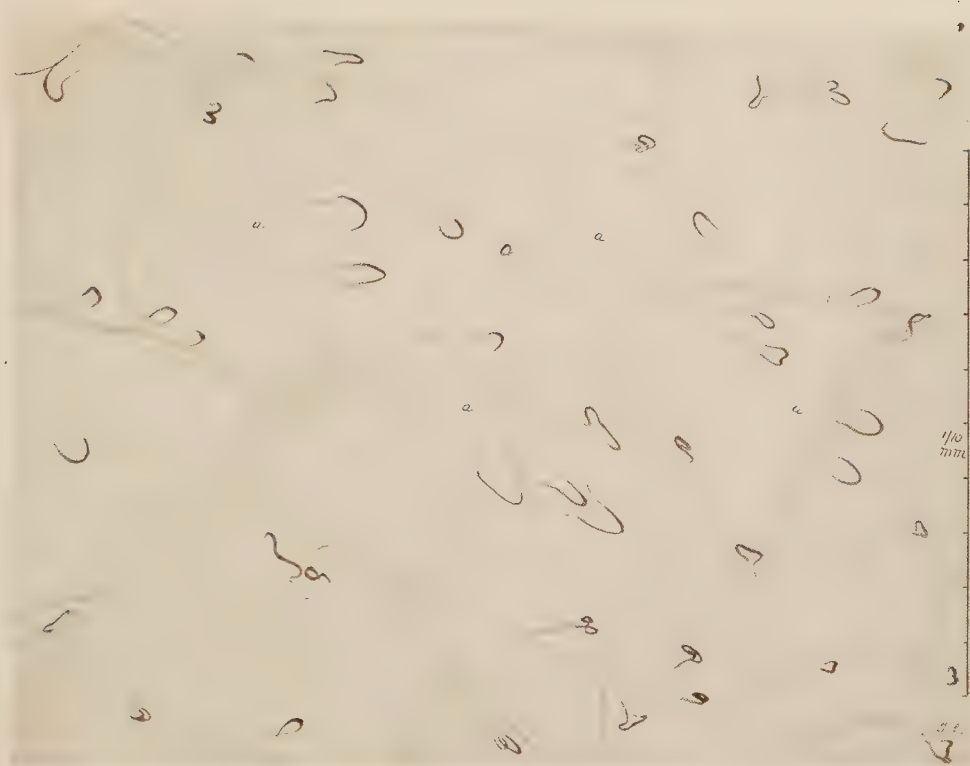
Fig. 5.

Fig. 6.
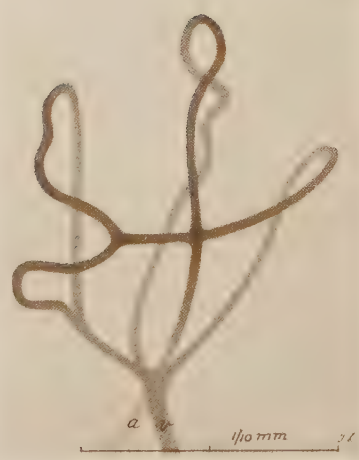
Fig. 7.

to each degree centigrade, the scale used in all references to temperature in this book,* is modified by means of the resistance box to suit the needs of the particular experiment. The form of junction and the method of using it varies with the purpose for which it is employed.

If the surface temperature of a particular skin area is desired, or if a comparison is to be made of skin temperatures at a number of points, each junction of the pair consists of a circular plate of thin silver foil, a few milli-meters in diameter ; to this plate two fine and insulated wires, one of copper
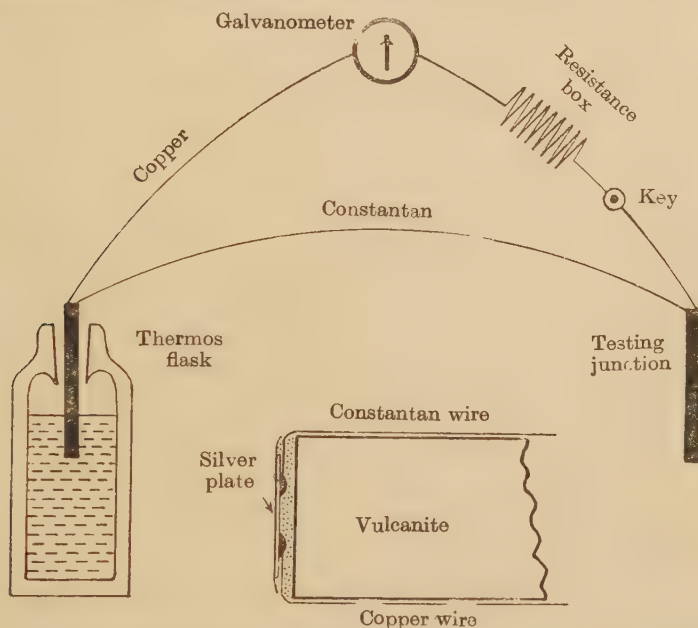
Fig. 8. A diagram showing the general arrangement of the thermo-electric couple when in use, and a diagrammatic section of one thermo-electric junction (enlarged).

and the other of constantan, are soldered and the plate is cemented to the flat end of a vulcanite rod or other convenient holder ; the two wires are carried up the rod and bound to it with silk, the whole, with the exception of the silver plate, being subsequently coated with insulating varnish. The vulcanite rod serves as a handle. One junction is placed in water at about 30 °C in the thermos flask, the other is applied to the skin which it is desired to test.

When this testing junction at room temperature is placed and held on warm skin, the beam of light shows a large and rapid excursion occupying a few seconds ; subsequently the beam moves much more slowly in the same direction and finally becomes stationary after a further delay of usually 15 or 20 seconds. The time of the first rapid deflection is controlled

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* For the convenience of those more accustomed to the Fahrenheit scale I have placed a conversion table at the end of the last chapter (page 294).

by the period of the mirror galvanometer, and diminishes as the excursion is less. The slower after movement is due to warming up of the skin under the contact. This warming up of the skin is not due chiefly to covering of the skin and a consequent retention of heat, but to the fact that when the silver plate at room temperature is placed on the warm skin it cools the skin, and the subsequent change is due to the skin gradually recovering its original temperature. This can be shown by moving the junction, when the beam of light has attained its final and stationary position, to an adjacent skin area ; in general the same final reading is then obtained almost immediately. To obtain an accurate and quick reading, the junction should be in contact with the tested skin for as short an interval as possible ; contact must be long enough to bring the beam of light to rest, it must be short enough to avoid such change of skin temperature as may result from covering the skin, or from interference with the superficial vessels. The procedure, therefore, is fully to warm the contact on an adjacent area or areas of skin, and then to move it quickly to its final position. The actual reading is thus obtained in a few seconds and is accurate. If the temperatures of several areas of skin are to be compared, and these temperatures do not differ by more than a degree or two, accurate readings may be obtained by moving the junction from one area direct to the next, checking the observations by repetition.

The same type of junction may be used in following changes of temperature in a given area and simultaneously in a control area, the junction being moved in one or more steps from one area to the other at regular intervals. Another method, useful on occasion, is to fasten junctions of the same type permanently over the two areas and to switch these junctions alternately into circuit. Skin so covered becomes a little warmer as a result ; although absolute readings of the natural temperature are not obtained, the error is not great and relative values are reliable.

Subcutaneous temperatures are taken by means of hollow needles. An insulated constantan wire is passed through a fine hypodermic needle and its end soldered at the point of the needle ; the needle is resharpened, sterilised and pushed through the skin so that its point lies two or more centimetres away from its point of entry and immediately beneath the true skin. This junction, lying at the point of the needle, is balanced against a similar junction of iron and constantan in a thermos flask. The introduction of such a needle itself lifts the skin temperature (from say 32°C) by 0·5 to 1°C ; it falls again towards its original point in 10 or 15 minutes.

The purpose of the thermometric method is to detect areas of skin in which the blood flow is increased or decreased, particularly to detect actual changes of flow, and to obtain an approximate idea of the extent of these changes.

In judging of change in flow, it is important to note the amount by which the original temperature lies below rectal temperature, for the lower the original skin temperature, the less significant is a small rise. When the original skin temperature lies within a few degrees of rectal temperature, a lift of 0·5 to 1°C means a very considerable increase in blood flow.

The absolute temperature of skin is an imperfect guide to blood flow ; much depends on room temperature and other circumstances. Thus the skin of the hands, though usually carrying more blood, is as a rule somewhat colder than is that of the exposed arms or trunk. The skin surface is relatively large in hands and feet, these therefore lose heat more rapidly.

Skin colour and its changes.—When the skin of healthy young adults of Northern European stock is depleted of blood, it is as a rule of a creamy white colour in most of those parts of the body that are clothed and submitted infrequently to pressure. This colour is modified in different individuals and in varying degree by the content of fixed pigment. In parts of the skin directly exposed to wind and light, the pigmentation is deeper, creamy whiteness giving place to deeper and familiar shades of yellow or brown. Upon this varying background the blood tints are suffused.

Blood colours the skin most vividly in the exposed parts, for example the face and the hands. In these parts and elsewhere the colour varies from place to place and from one individual to the next. The meaning of these differences in colour is explained in one of the final chapters of this book (Chapter XIX).

The vessels that give colour to the skin in greater or lesser degree are numerous. Skin varies much in transparency in different individuals and at different times ; as is well known, the colour even of subcutaneous veins of the limbs and trunk is often clearly visible. The more superficial the vessel, the greater will be its contribution to skin colour in respect of a given area that it presents to the surface. For this reason, and because in usual circumstances the vessels forming dense meshworks in the subpapillary region present a larger actual surface in the plane of the skin than do vessels at greater depths, these vessels contribute chiefly to skin colour. By usual circumstances, I mean in usual states of dilatation, such as are found when the body is at rest and the skin warm ; the statement made is true of the naturally suffused skin ; applied to the pale skin it is more doubtful. Pallor of the skin makes for transparency ; it is the pale skin that permits the colour of deep lying vessels such as the subcutaneous veins to appear ; when such a skin flushes, these vessels become less distinct or are lost to view. The more flushed the skin, the more do the superficial vessels contribute, not only because flushing greatly decreases transparency, but probably also because in vasodilatation, the area presented to the surface by the minute vessels is subject to the greatest absolute increase.

The class of vessel that contributes most to the naturally suffused or reddened skin is of chief interest ; it is now familiar to those who have worked much upon cutaneous vessels that, over most of the body surface, the subpapillary venous plexus is chiefly responsible (*43, 263*). An examination of injected specimens makes it obvious that this meshwork presents a far greater surface area than do the capillary loops or terminal arterioles, though it is true that it lies a very little deeper than the capillaries. To

exemplify from living skin, a careful drawing was made of every capillary and mesh of the subpapillary plexus covering 1 square millimetre of skin of the forearm, the vessels being drawn in a state of moderate distension. There were 68 capillary loops and the total length of the plexus vessels was about 20 millimetres. The total area presented by the capillaries to the skin surface was calculated to be 0·0095, and by the visible venous plexus 0·098, of a square millimetre, or about 1/100 and 1/10 of the whole area, respectively. Similar computations by Wetzel and Zotterman (*263*) agree with this estimate. A simple experiment confirms the contention that this plexus is mainly responsible for skin colour. If a glass slide is placed against the skin of the forearm and the vessels are watched microscopically while gentle and gradually increasing pressure is exerted, the skin pales long before the capillaries empty, and the most notable pallor develops at the moment when the venules of the subpapillary plexus collapse (*164, 263*); they are the first vessels seen to collapse. The more engorged the skin originally, the more striking is this demonstration. The final pressures, which obliterate the visible capillaries and proceed to collapse the terminal arterioles, increase the already existing pallor inappreciably. Thus, in the skin of the arm, which is representative of the relatively white skin of trunk and limbs generally, the subpapillary venous plexus contributes mainly to skin colour. The remaining vessels, especially the more superficial, will contribute in small degree. The part played by superficial venules is most manifest in the cheeks of many outdoor workers, for here these vessels are visible to the naked eye. In the hand and in the sole of the foot, where capillaries are most numerous, the share of the latter vessels in colouring the skin is more notable. Thus, it may be said that the depth of blood colouration in the skin is determined chiefly by the degree to which the minute vessels, and especially the venules, are swollen at the moment.

Depth of colour indicates the size of the minute vessels and throws no light on the rate of blood flow in the skin. Hands highly coloured but cold form a long familiar instance of congested vessels in which the blood moves slowly. A fact requiring more emphasis, and one to which both Ebbecke (*75*) and Dale and Richards (*59*) have recently drawn attention, is that an area of pale skin may be hotter and may give out more heat than one of a more usual warm colour. While depth of colour usefully gauges the size of the minute vessels, temperatures within certain limitations express relative rates of blood flow through them.

The tint of the skin presents a more complex problem. Tint depends chiefly on the relative amounts of hæmoglobin and oxyhæmoglobin in the vessels concerned. Blood enters these minute vessels in an arterial state, it leaves the last vessels that contribute to colour in a more venous state. The tint that we see is intermediate between the two, and depends in the first place upon the rate at which the blood flows through the minute vessels in question. Thus a bright arterial colour of the skin is usually significant of increased blood flow and the skin is found to be warm or hot ; a cyanotic

colour, in normal people, always means slow blood flow and the skin is cool'
or cold.   In skin that has natural warmth but is cyanotic, the arterial blood
is abnormal.

Rate of blood flow, however, is not the sole factor concerned ; the rate at
which the oxyhæmoglobin dissociates and the rate at which the oxygen so
liberated is used up by the tissues also affect the tint.   These last factors not
infrequently influence the colour of the skin in a direction opposed to that
exerted by the associated rate of flow.   Thus increased oxygen exchange
usually consorts with increased flow, and, while the former reduces, the
latter increases the oxygen content of the blood in the minute vessels.
Almost always factors other than rate of flow may be neglected, since the
latter more than offsets remaining influences.   This, however, is not always
the case ; the skin exceptionally may be red when little or no blood moves
through it (see page 145).   It follows that the tint of skin must be used
circumspectly in judging rate of flow, but so used, and especially when it is
combined with readings of skin temperature, it has great value.

The study of skin colour is particularly valuable in that information
obtained by means of it applies to large areas of skin.   The method and its
results are freely illustrated in subsequent chapters.

Other devices employed.—In many experiments described in this book,
a pneumatic armlet is employed, either to arrest the circulation to a limb,
or to raise the pressure in its veins.   For this purpose it is customary to
employ the familiar apparatus used in estimating human blood pressure.
The pneumatic cuff has a breadth of twelve centimetres and is connected
to the usual mercurial manometer of the U shaped type.   If, in a normal
subject, it is desired to prevent the passage of blood through the brachial
artery, this armlet is wrapped snugly around the upper arm and the pressure
within it is quickly forced to a point high above systolic blood pressure
(usually to 200-300 mm. Hg).

In using this simple apparatus, certain points are to be noticed.   For
example, since the pressure is not applied quite abruptly, it at first impedes
the blood flow in the veins and some blood collects in the arm before the
circulation is actually brought to a standstill.   Sometimes this is undesirable ;
it may be desired to lock up in the limb a natural amount of blood.   The
last may be accomplished approximately by throwing the pressure abruptly
into the pneumatic cuff from a large pressure reservoir.   By throwing a
known initial pressure upon the veins, or by first depleting these vessels,
either by holding the limb at various angles, or by first enwrapping it with
an Esmarch's bandage, various amounts of blood may be left in the arm
according to the object of the experiment.   In long continued observations,
the reservoir method also presents the great convenience that the pressure
is maintained ; it is unnecessary to watch the corresponding manometric
scale closely.

It is to be remarked that however high the pressure is raised in a 12 cm.
cuff on the upper arm, it will not completely block the circulation to the

limb.   A little blood enters through the arteries that supply the humerus, a little blood may ooze back through the corresponding veins.   The amounts are trifling and as a rule immaterial.   When a complete occlusion is essential, a wider cuff is used and it is applied to include the whole elbow joint.   In this circumstance all blood flow ceases between trunk and limb.

If a rise of pressure in the veins of the forearm to a given point is desired, this pressure is thrown into the 12 cm. cuff on the upper arm.   The blood collects under pressure in the veins distal to the cuff until it reaches armlet pressure ; then it begins to force its way through the obstruction and a stable pressure in the veins is soon reached.   Because it is important to be sure that there is no gross error in this method of raising venous pressure to a desired point, the matter has been investigated in the following way.   Subjects are chosen (*158*) in whom it is known that the amount of blood flowing to the limb is if anything below normal, this to ensure that filling will not be of unusual rapidity.   A vein in the forearm is opened and into it a cannula is tied distally.   The cannula is connected directly to a mercurial manometer by means of tubing containing 0·5 per cent. sodium citrate ; the manometer now registers the natural venous pressure, which, when the arm is dependent, may amount to 10 mm. of Hg.   The pressure cuff is applied to the upper arm in the usual way and the pressure within it is now raised to a given point. There is a prompt response of the venous manometer ; within a very short time this shows a reading equal, within error of measurement, to the pressure in the cuff.   The cuff pressure is now lowered and raised again to a different pressure level.   Examples of serial observations of this kind are given in the accompanying table.

Cuff pressure mm. Hg.	Pressure reached in vein in mm. Hg.	Rise occurs within (in secs).
0	10 (natural)	
22	21	15
32	32	18
40	39	39
49	48	38
58	57	34

Thus it is demonstrated that pressures up to 60 (or even 70) mm. Hg are reached in the veins within 40 seconds of throwing such a pressure on the upper arm ; and it is further shown that the cuff pressure is a very close measure of the final pressure within the veins.   To make doubly sure, it is the rule to apply the cuff pressure, not for 1 minute or less, but for 3 minutes.*

* When a high venous pressure (80 or 90 mm. Hg and, in the case of low systolic blood pressure, a lower pressure than these) is desired, this pressure should not be thrown upon the arm at once, but a lower pressure should at first be used, and this raised in small steps, each lasting a half minute or more.   Otherwise the initial high armlet pressure will impede considerably the blood flow to the limb and the full pressure desired will not be attained so rapidly in the veins.

The preliminary descriptions of method in this chapter are necessarily disconnected ; but they concern matters that are constantly relevant to the text of succeeding chapters, and it has seemed more desirable from the reader's point of view that they should here stand together, rather than that in later chapters they should form long parentheses, interrupting the thread of main arguments. Other methods of observation, other pieces of apparatus employed on occasion, are described with the experiments to which they directly refer.

FUNCTIONS OF THE SKIN VESSELS.

The cutaneous blood vessels bring to the tissue elements of which the skin is composed, those substances necessary for its nutrition and growth ; they carry away, in large part, products of skin metabolism. In performing these functions, their rôle corresponds to that of vessels supplying most organs and tissues of the body. They also supply materials to the secreting glands, sudorific and sebaceous.

The cutaneous vessels, like vessels in other situations, form an essential part of the mechanism of defence against injuries of diverse kind and, because the skin is particularly exposed to such, this mechanism is here developed in high degree. Thus, it comprises on the vascular side, as we shall see, a local nervous reflex, whereby an intense vasodilatation with greatly increased blood flow is rapidly called into play, not only at the stimulated point, but at threatened points around. This power of calling forth an intense and local reflex vasodilatation, with which the conjunctiva, another superficial structure, is likewise endowed, is seemingly non-existent in the deeply seated and more protected organs.

A further and highly important function of the integumentary vessels is found in the active part these play in regulating temperature ; by dilating and contracting they notably increase or decrease, and thus determine, the loss of heat from the body surface ; they are the only vessels of the body which work appreciably to this end.

There is some slight gaseous interchange between blood and the atmosphere through the skin, at all events in respect of carbon dioxide, but this function is unimportant.

The same vessels possess a further though less vital function, peculiar to themselves ; in races other than those deeply pigmented, they decorate and beautify the surface of the body, bringing to it warmth of colour, painting the cheeks of robust health, lighting up an emotional glow in the face of youth.

With these purposes, the arrangement of the vessels accords. It is in the most superficial parts of the skin, directly beneath the actively growing epidermal cells, that the final and most dense network of small blood vessels is meshed, spread out in a thin but very complete sheet, the plane of which is parallel to the outer surface of the skin. Through these vessels, lying a millimetre or less beneath the actual surface, certainly the greater part,

very probably the whole, of the blood brought to the skin ultimately flows, presenting in the flood time almost the greatest possible surface for the dissipation of heat.

This chapter, dealing as it does with anatomy and with method, and containing as it does broad statements of function, is preliminary to a discussion of later observations. We shall start by dealing with some simple colour reactions of the skin, and these will lead us on to a full survey of the effects of various forms of stimulation upon the cutaneous vessels, and to related problems. These studies will enable us in the closing chapters of this book to examine more accurately the various ways in which the blood flow to the skin is controlled and to account more fully for variations in cutaneous colour.

CHAPTER II.

THE WHITE REACTION. THE ACTIVE RÔLE OF THE

MINUTE VESSELS, INCLUDING CAPILLARIES.

PALLOR of the skin can be produced, as will be seen, in one or other of several ways ; but first we may consider the white reaction to a mechanical stimulus. If a blunt point is drawn with light pressure across the warm skin of the forearm or back, the skin pressed upon blanches as the point travels over it. This blanching results from a simple and temporary displacement of blood from the superficial vessels of the skin ; the natural skin colour returns and the white track left in the wake of the travelling point is obliterated almost as soon as it is formed. The skin over which the point has passed is now uniform in colour but, within a period varying usually from 15 to 20 seconds, the line of stroke again becomes visibly paler than its surroundings (*51, 196*). After usually a half or whole minute, this narrow band of pallor is of full intensity. It varies in conspicuousness in different subjects, being more readily provoked in the young ; it is naturally more vivid when the surrounding skin is flushed. Soon it begins to suffuse and is usually indistinguishable when 3, 4 or 5 minutes have passed.

A more certain method of eliciting this white reaction is to choose a flat ruler, 2 or 3 centimetres in breadth, its edges rounded off and smooth, and to draw the end of this ruler steadily, but not roughly, across the skin. The method is more certain because the force exerted by the observer is greater and therefore more easily and suitably graded ; the breadth of the ruler distributes this force, so that each point of skin traversed is but lightly stroked. The amount of pressure exerted is a little more than that necessary to expel the blood from the superficial vessels. The resultant white reaction is similar to that previously described, both in time relations and intensity ; it forms a clean cut and broad band across the skin (Fig. 9, page 27).

The precise nature of the mechanical stimulus that, after a short latent period, produces the white reaction requires further comment. The reaction does not seem to result from the pressure stimulating the vessels, neither is it an after-effect of their mechanical emptying ; for simple downward pressure exerted momentarily on the skin without stretching it, though it is sufficient or more than sufficient to empty the vessels, is not followed by

a white reaction. The blunt point or the end of the ruler must be drawn along the skin, and this drag places succeeding segments of the skin under *tension*. Tension seems indeed to be the effective stimulus, for I have found that if two fingers are placed an inch or so apart on the skin of a susceptible subject and the skin between them is lightly stretched, it is this skin rather than that with which contact has occurred which subsequently pales (*157*, *158*).

If a blunt point is drawn, not gently, but firmly across the skin, the reaction differs ; a narrow red band appears ; this is fully considered in the next chapter. In subjects that readily display the white reaction previously described, a firm stroke elicits the central red band, marking out the actual line of contact, and this is bordered by a distinct white halo (Fig. 9, page 27). The halo surrounding the line of a firm stroke, and the white band in the actual line of a gentle stroke have the same short period of latency and otherwise behave similarly ; there is no doubt that a common mechanism underlies the two. The skin that becomes the site of the white halo * has been untouched by the stroking instrument, but has nevertheless experienced tension, since, when the blunt point travels, the skin along the centre line is appreciably depressed and pulls on adjacent skin.

The stroke conveys its stimulus by placing the skin under tension and it remains to enquire upon what tissue element this stimulus acts. A remarkable feature of the white band that is caused by gentle stroking is the sharpness of its definition and the precision with which it maps out the actual area touched by the ruler. This precision is such as to suggest that the effect is not produced passively by arterioles that supply areas of skin of more than a square millimeter or two in extent ; it first drew our attention to the minute vessels of the skin and intimated to us (*51*), as it did to Müller (*196*), that the reaction might be due to active contraction of the vessels responsible for skin colour.†

Lapinsky (*147*), who also studied this reaction, was reluctant to come to a conclusion opposed by contemporary physiological thought, and he suggested that the white reaction is due to involuntary muscle fibres in the skin, namely, those which erect the hairs. Now it is true that these readily contract under the stimulus of stroking ; but the white band is not due to them. The response of these muscles, when it occurs, and that is by no means invariable, is quicker. Often the goose skin effect is easily seen and appears before the pallor sets in ; it subsides quickly, and while the pallor is at its height or is still growing in conspicuousness (*51*). The contraction of these muscles exerts little or no influence on the calibre of the skin vessels, and no doubt remains that the white reaction is independent of this muscular mechanism. We return, therefore, to the vessels themselves.

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* A white halo arising in a different manner and persistent is described in Chapter XIII.

† I retain this our original argument of sharpness of definition as suggesting minute vessel activity despite Krogh's criticism of it (*137*, *page 32*). Krogh states that the meshes of the subpapillary networks are small enough to render such an argument invalid. The criticism assumes too readily that we spoke of capillaries in the strict anatomical sense.

Reduction in the size of the vessels that are responsible for skin colour
has manifestly happened in the white reaction ; and it might be natural
to attribute this change to contraction of the arterioles supplying the
corresponding area of skin ; for such arteriolar constriction could be said
to lower the distending pressure in the minute vessels and these would tend
to become emptier as a consequence. But we were reluctant to accept such
an explanation for the reason stated, namely, the sharpness with which the
area stimulated is subsequently marked out by the reaction ; there is the
additional argument that obliteration of the brachial artery does not empty
the minute vessels nor produce pallor of nearly the intensity that is seen in
the white reaction. There remained the possibility that the reaction is
due, not to a passive effect of arteriolar constriction, but to an active change
in the minute vessels themselves.

The following experiment was devised (*51*) finally to differentiate between
the two last causes. An armlet is placed on the upper arm of a subject, the
skin of whose forearm is known to yield a conspicuous white reaction to a
stroke, and a pressure of 250 or 300 mm. Hg. is thrown abruptly into the
armlet from a large pressure reservoir. The flow in the brachial artery and
veins is instantly obstructed by this procedure and the onward flow in the
capillaries of the lower arm rapidly ceases. Since, at the moment of
compression, the pressure within the arteries is higher than in the veins. flow
does not cease at once ; but it does cease, as direct observation of the
capillaries of the nail bed shows, within a very short time, namely within
$\frac{1}{2}$ to 1 minute (Neumann *199*, and personal observations). Kendrew (*129*),
working in my laboratory, found that the pressure in the veins rises for about
these periods after the pressure is applied. The pressures in the vessels of
the arm as a whole enter a state of general equilibrium and this state is
subsequently maintained. If the two arms are now stroked simultaneously,
the white reaction appears on both. Within observational error, it appears
simultaneously on the two arms, is equally vivid on the two, and fades away
in much the same time. Briefly, the reaction is not affected when the
circulation in the limb is stopped. A white reaction may be obtained in
the skin of such a limb when its main vessels have been firmly compressed
for periods of 5, 10 or sometimes even 15 minutes.

It is to be noted that the occluding pressure should fall abruptly on the
vessels. The same result can be obtained by raising the pressure
more gradually, though it is less certain ; for, if the pressure rises gradually,
the veins are obstructed some while before the arteries, and so venous pressure
is raised in the arm and interferes in greater or lesser measure with the visible
result. In a properly conducted observation the colour of the skin and the
distension of the limb veins should be the same in the two arms at the instant
when the brachial artery of one actually becomes closed.

The appearance of a white reaction to stroking, when the circulation
has been brought to rest (Fig. 10, page 27), is an event of prime importance,
for it is incompatible with a belief that the reaction is due to stimulation of

Fig. 9.   ($\times \frac{2}{5}$).   *White reaction and red and white reaction.*   The end of a
       flat ruler has been drawn horizontally across the skin of the back,
       and two firm strokes with a blunt point have been laid down vertically.
       The simple blanching produced as an after-effect of the first, and the
       central red lines bordered by blanching, produced as an after-effect
       of the second, were photographed three minutes later.

Fig. 10.   ($\times \frac{1}{2}$ approx.).   *White reaction with circulation stopped.*   In a sub-
       ject whose systolic blood pressure was 110 mm. Hg, the circulation
       to the limb was arrested by throwing a pressure of 200 mm. Hg into
       the pneumatic armlet.   Two minutes later the arm was stroked
       transversely in two places with a flat ruler.   The white reaction shown
       was photographed four minutes after the occlusion of the vessels.

Fig. 9.
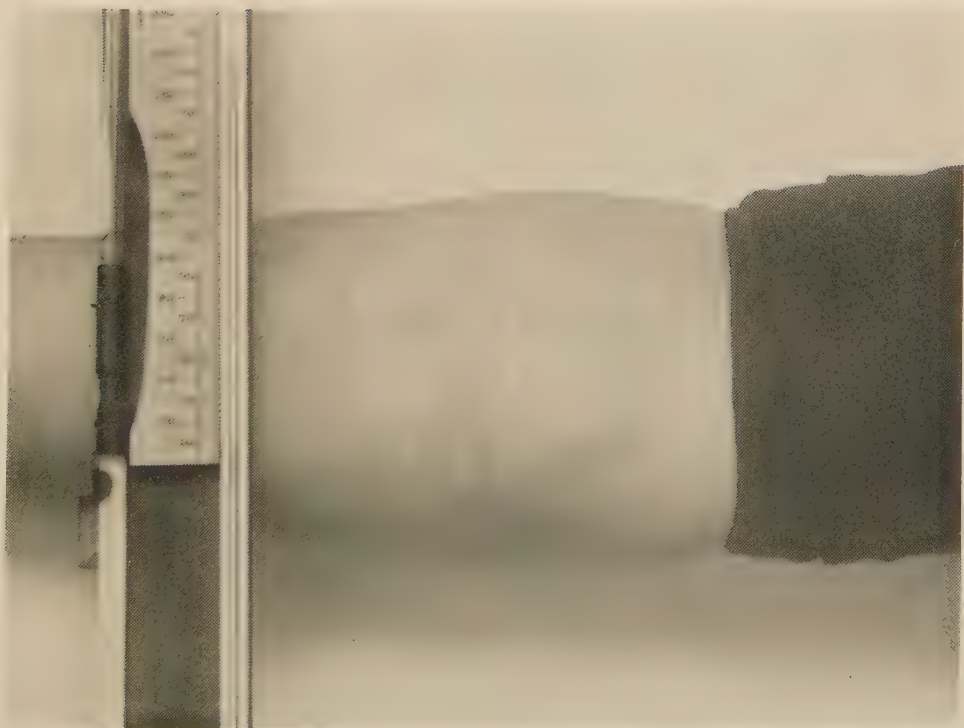
Fig. 10.

the arterioles. It proves that the walls of the minute vessels contract and expel their contents. When the circulation has been stopped, an arteriolar contraction, if it affects the minute vessels at all, can only increase their contents. The reaction occurs in the walls of those vessels that are responsible for skin colour, and not in the walls of vessels conveying blood to these. It is an active and not a passive effect in the vessels that are under examination. This observation, made 11 years ago, and the conclusion then based on it that " we are forced to regard the tissue elements immediately surrounding the capillary blood and forming an essential layer of the capillary wall as the source of the reaction," is to be emphasised.

The experiment has recently been confirmed by Carrier (*43*), and by Parrisius (*203*), who have determined that each member of the minute vessel group is involved, by observing the skin microscopically before and after stroking it when the circulation to the arm is at a standstill. They saw the terminal arterioles, the capillaries and the minute venules into which these lead, namely, the first collecting venules and the subpapillary plexus (collectively, the minute vessels), diminish in size, observations which I have also since made. We now know that the skin colour of the forearm is due more to vessels of the last than to those of the first orders, and it might be said that our original conclusion that the *capillaries* are actively involved was not warranted by the naked eye observation, since this presented evidence of contraction of minute venules rather than of capillaries proper. This standpoint would be pedantic. Our conclusion was actually applied not to capillaries but to the vessels responsible for skin colour without differentiation, for at the time of writing we used the term capillaries in that sense.*

Further evidence brought forward at the same time (*51*) harmonises with the conclusion formulated that the minute vessels actively contract. If the skin of the normal hand or forearm is gently pressed upon and the pressure rapidly withdrawn, the area mechanically blanched quickly resuffuses with colour ; blood flows in from the neighbouring vessels of the same order. The colour returns to the edge of the blanched area first, and later to its centre. Doubtless the empty vessels are also in part filled from deeper vessels, but that the inflow is largely from surrounding vessels is known because it can be seen to occur under the microscope, and because the same event happens after the circulation to the limb has been stopped. An additional reason for the same belief is that if the test is carried out in the cyanosed limb, it is cyanotic blood that re-enters and not blood

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* In their elemental structure all these vessels are the same, if we neglect scattered muscle cells said to be present on the terminal arterioles (*231a*) ; so far as we know they are all alike in their physiological functions, contracting and dilating in response to similar influences (see page 204), supplying, through their walls, nourishment to the skin ; even recently Vimtrup (*256*) refuses a closer definition of capillaries. There is something to be said for this older point of view, but in view of the obvious and present possibility of confusion in terms it seems now desirable for descriptive purposes to restrict the term capillary to the capillary loop. In this connection it is to be remembered, however, that more direct paths exist between the arterial and venous system, as described on page 2, and that to some of these the term capillary is certainly applicable from an anatomical standpoint.

from heavily coated arterioles, for this would be of arterial colour. The venules of the skin that chiefly give it colour form a very freely anastomosing mesh or network, and the blood is readily displaced by pressure from one area to the adjoining areas and as readily returns.

If we stop the limb circulation without emptying the veins and create two blanched areas, the one purely mechanical and the immediate effect of light pressure, the other a reaction occurring after a latent period to light stroking, these subsequently behave differently. The area blanched mechanically begins to suffuse immediately on the release of pressure and in a second or two is quite unrecognisable. The duration of the white reaction is measured in minutes. Whether the circulation has been obstructed or not, this blanched area remains for a long time ; the vessels may remain empty for as long as five or more minutes. Why is there no flow into this area from neighbouring vessels of the same order ? There can be but one answer. It is not that the supply is absent ; it is that the empty vessels resist the inflow ; they do so because they are in a contracted state.

The reasons for placing these crucial observations in the foreground are several. The first will be apparent at once ; the observations are undertaken upon the human subject and the conclusion applies to *human* capillaries and venules, thereby adding to its value. Secondly, the actual observations are of the simplest character, easy to repeat and demonstrate ; for this reason and because the appearances are manifest they are the more convincing ; likewise their interpretation is freed from many minor sources of error ; for there is in this case the minimal disturbance of the living structures concerned in what is evidently a delicate reaction. Thirdly, because they serve to illustrate the truth that a conclusion is suggested or may be reached from every distinct phenomenon observed, however simple or trivial such observation may at first sight seem, and that sometimes, as here, the conclusion may possess a far reaching application, if based on observations properly controlled. Fourthly, because the conclusion has proved unassailable ; it formed the first of those demonstrations that during the last decade have converted physiologists to their recent and now almost universal belief in the important part played by the capillaries in controlling the circulation.

The actual conclusion was one that had already been formulated very many years before, but remained inacceptable to physiologists in general. That was so for two chief reasons. On the one hand because most of the observations, pointing to this conclusion, insufficiently discriminated between active and passive effects. On the other hand because the observations were carried out microscopically on amphibian tissues, easily susceptible to external conditions of moisture, temperature, and injury, unseen or unheeded ; and because the experiments required for their success a delicate and most carefully guarded technique ; for these reasons they were highly subjective observations difficult to repeat or to demonstrate, and open to the suspicion of fallacy.

The contraction of the minute vessels in response to tension after a short period of latency, appears to be the direct result of stimulation of their walls. It is independent of nervous reflexes, central or local. Thus, Ebbecke (*75*) saw it occur on skin to which the nerve supply had long been lost, and Carrier (*43*) on skin locally anæsthetised. I have myself seen it in skin to which the nerves have been cut surgically and allowed to degenerate (*167*), a white reaction being obtained across sensitive and insensitive skin ; the two parts of the reaction are quite indistinguishable.

The contraction response of the minute vessels is apparently not peculiar to those of the skin, for a white reaction, so Ebbecke (*75*) states, may be produced similarly on the surface of mammalian viscera, such as the liver, spleen and kidney. Florey (*85*) finds that the capillaries leaving the arterioles of the pia mater for the cerebral cortex contract to mechanical stimuli, but that all the capillaries do not so react. Personally I have been unable clearly to elicit the white reaction upon the surface of the cat's liver or spleen, but have seen it on the kidney.

We can only speculate at the present time as to the useful purpose that this function may serve. In the case of the skin, alternate stretching and relaxation occur as an accompaniment of bodily movements, and the reaction described may beneficially divert some blood to the muscles (*157*). This possibility would seem, however, too trivial to form a satisfactory answer to our search for the purposive nature of the response. It is possible that the main object fulfilled is protective. It is conceivable that a rise of internal pressure may act as does an external stretching force, and that a resultant increase of minute vessel tone may guard these vessels from over distension, and even at times save their walls from rupture ; such a response would at least tend to curb the increased blood flow through the minute vessels (see Chapter XIII). It is to be remembered, however, that we have no proof that an internal stretching force acts in the manner suggested.

Adrenalin and pituitary extract.*

A second and reliable method of producing a white reaction is to apply adrenalin or an extract of pituitary gland to the vessels of the skin. Thus, if a few drops of a 1 in 30,000 solution of adrenalin are injected immediately beneath the skin, or intradermally, the area of skin so treated blanches completely after a latent period of 15 to 60 seconds. A sounder method is to place on the skin surface a small drop of 1 in 1,000 adrenalin solution, and to prick the skin through this drop of fluid with a sharp and clean needle. The drop of fluid is then removed and the skin watched ; it soon pales intensely around the point of puncture, in response to the minute amount of substance introduced, and a circular area of blanching of a few millimetres diameter is seen (Fig. 11, page 39).

This reaction, as we were able to show, is given with equal intensity by skin previously deprived of its circulation for periods of 5 or 10 minutes in the manner previously described (*51*). That adrenalin is capable of con-

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* Parke, Davis & Co.'s adrenalin and Burroughs & Wellcome's 17% pituitary extract (called infundin) have been used in all our observations.

stricting the vessels of the human skin has long been known, the substance has been used time and again to check oozing from abrasions and cuts ; but it was not known, until the simple observation here described was made, that adrenalin produces active constriction of the smallest skin vessels, in fact it was very generally held that its constrictive effects are solely produced by its action upon the arteries and arterioles. The experiment described permitted no other conclusion, but that adrenalin is capable of acting directly upon the minute vessels that are immediately responsible for the natural skin colour.

Pituitary extracts have a similar power, as Sacks and Grant and I (*165, 223*) have frequently been able to show by similar tests.

That all the vessels comprised in the term minute vessels are affected has been determined by examining the skin microscopically. Thus Carrier (*43*) and also Heimberger (*112a*) by introducing a minute quantity of adrenalin solution into the skin in the neighbourhood of a single capillary loop, observed a primary and independent contraction of this loop. This and microscopic examination of the skin in which the circulation is at a standstill, demonstrate that adrenalin and pituitary extracts cause active contraction of terminal arterioles, capillaries and minute venules. The adrenalin acts directly on the wall of the vessel, the reaction being equally vivid in skin deprived of its nerves (*28, 167*).

The force that the minute vessels are capable of exerting.

The examples now cited are sufficiently simple and adequately illustrate the independent power of the smallest vessels to contract. Now, if the minute vessels possess this power, and there is no longer any doubt that they do, they are clearly capable of influencing nutrition in the tissue elements that they directly supply. It becomes manifest that the older explanations of both local and general changes of blood flow, which based themselves exclusively on the state of the muscular arterioles, are no longer justifiable ; the tone of the minute vessels also must be considered fully.

There is evidence that the force exerted by these vessels is very far from negligible. In the human skin this force has been investigated in the following manner (*157, 158*). A white reaction of the forearm skin is obtained in one of the two ways described, and pressure is now thrown and maintained upon the veins of the upper arm. As we have seen (page 20), the venous pressure rises fully and quickly in these circumstances to the point that the manometer registers. It will be evident that the pressure within the minute vessels is thereby raised, and that it is raised to a point lying somewhere between the armlet pressure and the systolic pressure in the arteries. By raising armlet pressure to different points, we may produce different pressures within them, the minimal possible values of which are known ; and we may test the power of the contracted vessels of the blanched area to withstand such pressures. When these vessels, of such skin as that of the arm, are contracted in response either to stroking or to adrenalin, they are able to resist minimal distending

pressures of as much as 80, 90 or 100 mm. Hg (Fig. 11, page 39). Judged in this way, the intensity of contraction provoked by stroking is in general less than that induced by adrenalin. Arguing from the last particularly, it may be said that the pressures resisted equal, if they do not exceed, any pressure that can possibly be exerted on the minute vessels from the arterial side.

In direct support of this statement is the following simple experiment. Adrenalin is punctured into the forearm and, when the skin has become fully blanched, this blanched area is surrounded at a distance of 2 cms. by four drops of 1 in 300 histamine solution.* Before long the blanched area becomes surrounded on all sides by a brilliant scarlet flare, due, as will be seen in Chapter V, to an arteriolar dilatation. The intensity of the flare may be judged by the temperature of the skin, which in the immediate vicinity of the blanched area in one such observation rose from 31·8° to 34·4°C, indicating a very greatly increased blood flow ; yet the adrenalin pallor was not in the least diminished. The widening of the arterioles, probably almost to their full capacity, fails to force open the capillaries and minute venules held contracted by adrenalin. Now it may be said in criticism that, in the blanched area, the terminal arterioles are also held shut by adrenalin and that the arteriolar pressure is therefore unable to penetrate to the capillaries and venules beyond them. But it certainly penetrates to venules of the same order in the immediately surrounding skin and these are in free communication by anastomosis with the vessels of the blanched area. A free path is actually open between arteriole and closed venule, yet the latter remains closed. The subject now exercises so vigorously that systolic blood pressure is observed to rise to such levels as 200 mm. Hg ; the blanched area still remains unchanged, although this procedure probably brings to bear on the minute vessels in the affected area the full force that the heart is capable of exerting on them in the normal subject.

From such observations it becomes clear, therefore, that blood will fail to enter the minute vessels of the skin, when the heart beat is greatly augmented and the arterioles are widely opened up, provided that the minute vessels choose by vigorous contraction to deny it entrance.

That forces of this order can be exerted by the minute vessels becomes more intelligible when their diameters are borne in mind. On purely physical grounds we know that the contractile elements will work with greater and greater effect as the vessel is smaller. In estimating the strength of contraction, the circumstances in which the force is brought into play must be considered. When adrenalin is punctured into the skin, the walls of the minute vessels contract upon and expel their contents. The pressure required for this purpose is not great, since the pressure in such vessels lying level with the heart is not high.

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* This strong solution is deliberately chosen so that a maximal effect may be obtained. The result is the same if a reactive hyperæmia following 10 minutes arrest of the circulation (see Chapter XI) is substituted for the histamine flare.

A priori, the maximal pressure that contracted and closed vessels are able to resist is not necessarily, or even probably, a measure of the maximal pressure that the same vessels can develop when already open. That this is here actually the case may be shown, for if the venous pressure is raised to 80 or 90 mm. Hg before adrenalin is applied, the white spot does not appear. An adrenalin contraction of the vessels becomes perceptible when such lower pressures as 40 to 60 mm. Hg are employed. In the circumstances of the experiment the vessels are much dilated before they are called upon to contract, and thus work at a disadvantage.

Judging, however, from the distending pressure that may be overcome under these conditions, it is probably correct to state that, when the body is at rest, the minute vessels are capable of emptying themselves in most, though not all, physiological circumstances. Thus, if adrenalin is punctured into the dorsum of the foot in a man standing at rest, blanching does not appear, for the venous pressure in the foot in these circumstances is too considerable.* After a little while, if the blood is wiped upwards out of the dorsal veins of the foot or if a few steps are taken and the veins of the limb thus emptied by muscular movement, thereby lowering the pressure in the veins of this territory, the blanched areas at once appear at the sites of puncture, and are subsequently maintained (*157, 158*).

To sum up, simple observations upon man are recorded, and these demonstrate that the minute venules of the skin all possess contractile power ; they further show that this activity is by no means negligible, for, when fully called into play, it may suffice to impede or stop the blood supply to the corresponding skin.

The method of testing the capacity of the minute vessels to contract against a venous pressure raised artificially, here described, has been used, as will be seen in later chapters, to compare the state of these vessels, in respect of tone, in different parts of the body and in different subjects.

Historical.

A chief and stated object of this book is to record phenomena to be observed in man ; it is not within its scope to review in detail experiments on lower animals that may have led to similar physiological conclusions, unless such experiments can clearly claim priority, and form the starting point of work on human beings. Thus, it would be misleading to describe an observation upon man and to couple it with a conclusion, if a similar or identical observation and corresponding conclusion derived from animal experiment at an earlier date were to receive no mention.

The experiments on human skin here described, and those on active dilatation in the next chapter, were in actual fact independent observations and, as already indicated, led to a conclusion in conflict with contemporary physiological belief. Nevertheless there existed in previous writings statements of fact and heterodox views with which these observations on man seemed best to harmonise. Thus, Stricker (*238, 239, 241*), who worked as early as 1865 upon the excised nictitating membrane of the frog's eye, a transparent structure, believed that he saw spontaneous contractions of its finest vessels, and occasional responses of these to stimulation. Although these observations were confirmed in the next few years by those of Rouget (*220, 221*), Golubew (*99*), and Tarchanoff (*244*), doubt remained as to their precise meaning and opinion diverged as to

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* Calculated hydrostatically it amounts in a man of medium height to 90 mm. Hg, though as Recklinghausen (*213*) and Hooker (*119*) have shown, this full hydrostatic pressure is not actually attained unless there is complete flaccidity of the muscles.

the nature of the contraction, whether local or general, and as to the tissue elements involved. Rouget's description, in amphibians, of spindle cells encircling the capillary wall by outjutting processes, cells held by Mayer (*187*) to be transitionally continuous with the contractile wall of the muscular arterioles, lent support to the hypothesis of active contraction. In this country Roy and Brown (*222*) were the strongest and earliest advocates of this view, because, when they submitted capillaries to external pressure, they were unable to determine a sufficiently close relationship between the change in the vessel's size and the pressure exerted. In 1903 a very important paper was published by Steinach and Kahn (*233*); these workers confirmed and extended Stricker's observations; they saw local contractions of capillaries; they saw blood forced simultaneously from both ends of a single capillary responding to stimulation, an observation that precluded a flow dependent on pressure change in the parent vessels. Blood corpuscles lying in the capillary at its contraction were seen to be squeezed out of shape. The latent period of contraction was given by them as several seconds. These writers reported similar events in the omental vessels of mammals.

It seemed to us at the time our article appeared (1917) that these observations had received too slight an attention, and that they really shifted the onus of proof to those who held the capillaries to be non-contractile. Subsequent events have shown that view to be correct. In 1918 Dale and Richards (*59*) published their well known paper, in which they described a number of blood pressure phenomena resulting from the injection of histamine, acetyl-choline and adrenalin. A searching but intricate analysis of the corresponding reactions led them to the belief that minute vessels beyond the arterioles react. The most recent work is that of Krogh (*135, 136*) in which many of the earlier observations on transparent tissues are repeated, confirmed and extended.

The tissue elements concerned in capillary contraction (Rouget's cells).

Observations upon man have thrown no light upon this question, but it is desirable that it should be discussed briefly.

In 1873 and later, Rouget (*220, 221*) examined the capillaries in transparent tissues of amphibia and described certain cells lying on their walls; these cells possess elongated nuclei and their protoplasm is described as prolonged into a number of processes that enwrap the capillary wall. He stated that he had seen these cells contract. Mayer (*187*), who examined the same cells at a much later date, considered that they formed a complete transitional series with muscle cells on the walls of small arterioles. Recently Vimtrup (*255*) has described these cells in more detail, and has found cells that he regards as equivalent to them in mammals and in the vessels of human skin (*256*). Vimtrup has watched these cells in amphibians during active contraction of capillaries and believes, with Rouget and others, that they are the active agents. The conclusion depends upon minute observation; thus the first change of shape in the capillary wall is stated to occur always at the point where the Rouget's cell lies, and distortion or actual folding of the endothelial cells, such as might be expected to result when they are grasped by the processes of the Rouget's cells, is described. Other observers, however, describe contraction of the capillary wall as a whole, as did Stricker. Zimmermann (*272*), who terms the cells "pericytes," believes them to be the forerunners of smooth muscle cells and themselves contractile. Marchand (*185a*) identifies them with "adventitial cells" derived by subdivision and separation of endothelial cells. Spalteholz (*231a*), after examining Vimtrup's preparations, fails to distinguish them from connective tissue cells. Clark and Clark (*48, 49*) describe the Rouget's cells as derived from stellate connective tissue cells, and they picture these as wandering onto the living capillary walls; here, at the end of their migration, they flatten out, adapt themselves to the shape of the capillary, and settle down. Clark and Clark do not believe these cells to be active agents in producing capillary contraction. They describe the movement of the endothelial wall as an independent movement, which may carry the Rouget's cell with it or may lead to the appearance of a definite space intervening between Rouget's cell and endothelium. Thus, there is considerable conflict of evidence and opinion, and both the derivation of Rouget's cells and their relation to capillary contraction must be regarded as still undecided (see also Florey and Carleton (*87*) and Tannenberg (*243a*)).

Chapter III.

Red Reactions Induced by Mechanical Stimuli.

The local red reaction to stroking.

The last chapter has dealt with the white reaction to gentle stroking or stretching of the skin. The red reactions that follow stroking, and which are now to be considered, follow mechanical stimulation of greater or much greater intensity and, as we shall see, these are quite differently caused. When a red reaction occurs, no trace of white reaction appears on the line stroked ; to the white reaction therefore we shall not often refer again, for this effect of stroking is swamped by the more pronounced and opposite reactions now to be described.

When the skin is firmly stroked with a bluntly pointed instrument, a subsequent red reaction along the line of pressure is invariable (Fig. 9, page 27). It begins to appear in about 3 to 15 seconds after stimulation (*51*), a latent period somewhat shorter than that of the white reaction, reaches its height in a half to one minute and fades very gradually. It may be gone in a few minutes or it may last for a half hour or longer. The intensity of this red band and its duration increase with the strength of stimulus employed ; they increase if the stimulus is repeated. As in the case of the white band, it is remarkable how this red reaction marks out the skin that has been stimulated, and how clean cut are its edges. The red line when it first appears is bright in colour, but later gradually assumes a definitely bluish tinge.

It is due to widening of vessels that normally colour the skin and, as microscopic examination of the skin shows (*43*), all the minute vessels are involved. Distension of these vessels may be brought about in one of several conceivable ways : the arterioles that feed them may relax, the minute vessels may themselves relax, the veins into which they pour their contents may constrict, or lastly the reaction may be caused by a combination of these events.

The skin involved corresponds so accurately to the line of pressure and its margins appear so clearly ruled, that it is difficult to resist concluding that the vessels mainly determining the reaction belong to the smallest orders. It is inconceivable that arterioles supplying more than a square millimetre of skin, or that veins having more than a corresponding territory, could be responsible. This is the argument that Müller first used and that

formed our own independent starting point at a later date (*51, 196*). The similarity in form of the white and the red band in itself speaks strongly for primary involvement of the vessels of the same order in the two circumstances. Constriction of the deep veins is rendered unlikely by the crisply outlined reaction, such as can be seen both macroscopically and microscopically in the collecting venules and subpapillary venous plexus. Although there are free lateral outlets for the blood in this plexus, it remains distended sharply to the margin of stimulation. That the effect does not follow passively from relaxation of arterioles of any considerable size is also suggested by the definite tendency of the red band to become bluer once it has appeared.

The view last referred to, and one which long held the field, was finally disproved by bringing the circulation of the limb to a standstill as a preliminary (*51*). A dilatation of arterioles in these circumstances could withdraw blood from the minute skin vessels, it could not fill them. Yet they become filled in response to a firm stroke and, if there is a full content of blood in the limb at the time, the line of stroke stands out sharply and soon becomes livid (Fig. 12, page 39).

The same observation also excludes a constriction of the deep veins as the cause, for although this might conceivably force a little blood to flow backwards towards the surface, it could not produce the vivid and sharply outlined reaction that is seen. The vividness of the red band, produced when the circulation is at a standstill, depends largely upon the amount of blood left in the vessels of the arm at the instant the arteries are occluded ; to obtain a striking reaction, a preliminary pressure of 30 mm. of Hg should first be thrown into the armlet, the pressure in which is then raised abruptly to 250 mm. when the veins have become congested ; after a period of minutes during which the distribution of blood in the limb readjusts itself, the stroke is given.

It is perfectly clear from these observations that the mechanism is mainly one in which there is an active and not a passive relaxation of the minute vessels themselves.

It has been pointed out by Carrier (*43*), that the line of reaction appears red on an arm first rendered bluish by exposure to cold. The same holds good in the case of an arm rendered purple by venous congestion, a method that is more satisfactory and one that I have repeatedly used. In this test a pressure of 70 mm. of Hg is thrown upon the veins of the upper arm and maintained there for 3 minutes ; at the end of this time the arm is deeply cyanosed. A firm stroke upon the skin of the forearm is now followed by the appearance of a line, which by its redness contrasts conspicuously with the surrounding purple skin ; this redness is not temporary, it is maintained.

The last point has its importance. If an arm is rendered cyanotic by congestion, and the blood is then mechanically displaced from the superficial vessels, it might be thought that new blood would flow in mainly from the arterioles and that this blood would be arterial in colour ; thus, a temporary

Fig. 11. ($\times \frac{2}{3}$ approx.). *White reactions resulting from pituitary extract and suprarenal extract, resisting venous congestion.* Needles were lightly thrust into the skin through three drops of pituitary extract and through three drops of adrenalin solution (1 in 1,000) on the forearm. Some minutes later, when full blanching had occurred at the sites of puncture, the venous pressure in the arm was raised in steps, 30, 50, 70 and 80 mm. Hg, each maintained for 1 minute. The white spots were then photographed. The actual sites of puncture appear as red dots. Systolic blood pressure of subject 120, diastolic 85 mm. Hg.

Fig. 12. ($\times \frac{2}{3}$ approx.). *Purple line of stroking and purple spots of histamine compared.* In a subject whose systolic blood pressure was 125 and diastolic 95 mm. Hg, a pressure of 30 mm. was thrown on to the veins of the arm for a half minute ; the armlet pressure was then raised to 190 mm., thus arresting the circulation. Three minutes later the skin of the forearm was stroked firmly and three histamine punctures (1 in 3000) laid down. The purple line and small circular spots developed simultaneously and were photographed at the sixth minute.

Fig. 11.

Fig. 12.

reddening might indicate simple replacement. If the redness is continued, on the other hand, then it is evident that the rate of blood flow has been increased beyond that prevailing in the surrounding skin. Actually, when blood is displaced from a passively congested skin, that which flows back is not red but cyanotic.

Another, though more occasional evidence of increased blood flow is that if the stroke is made on the arm without interference with the limb veins, a thermo-electric junction may detect a slight rise of temperature subsequently along the line of stimulation. If the stroke has been moderate in force this temperature rise is absent or trifling in amount ; if firmer the temperature may rise 0·5°C or more.

It has been thought that such phenomena indicate involvement of arterioles. A slight contribution by dilatation of arterioles of larger size than the terminal arterioles cannot, perhaps, be excluded, though it is manifest from evidence already given that the reaction is one mainly confined to the minute vessels themselves. The increased flow of blood to the skin so effected is possibly due to dilatation of vessels of the last order, a question discussed more fully in Chapter XVI.

We conclude that the local red reaction, properly so called, to stroking is due to an active dilatation of the minute vessels, namely the terminal arterioles, capillaries and minute venules ; this is as far as the question can be taken at present with certainty. (See further remarks on page 44.)

The red line appears without the intervention of the central nervous system or of a local nervous reflex ; it is seen equally well on skin to which the nerves have been cut and in which these have degenerated (*75*, *164*).

The red line in response to stroking is not peculiar to the skin, but may be elicited on the surface of such organs as the liver and spleen in animals, a fact pointed out by Ebbecke (*75*) and one that I am able to confirm ; from Florey's descriptions (*85*) the vessels on the surface of the brain show a corresponding reaction only on occasion.

The spreading flush or flare.

When the skin is susceptible, when the stroke stimulus is unusually strong, or when it is repeated a number of times along the same line, the visible reaction is no longer confined to the line of stroke, but spreads beyond it. The red line, already described, appears first and, after an additional delay of perhaps 15 to 30 seconds, the neighbouring skin begins to be tinged with colour. This flush increases in intensity and spreads for a greater and greater distance from the line (Fig. 14, page 49). Its edge may extend one, two or three centimetres from the midline of the reaction ; exceptionally this distance may be increased to as much as ten centimetres.

The spreading flush or **flare**, as I shall subsequently call it, has peculiarities that at once distinguish it. It is of scarlet colour, contrasting with the purely local reaction when this assumes, as it soon does, a bluish tinge.

The colour of the flare is maintained almost if not quite in its pristine freshness until it fades, and this happens much earlier than does the fading of the local red line. The blood contained in the skin vessels responsible for this flare does not stagnate but remains of arterial tint. The colour intensity of the red line is uniform at any given moment ; that of the flare is not. At first the flare is ill-defined, diffuse, and often crenated at its edges, becoming less intense as it is traced outwards from the centre. Later, during the period of fading, it is speckled. The speckles are at first most conspicuous at the edges of the flare, later they are seen throughout it (Fig. 15, page 49). The margin of the flare is ragged at this stage and numerous small islets of colour are often found outside the main area involved. The brighter the original flare, the longer does it last.

These appearances led both Müller (*196*) and ourselves (*51*) to conclude that the two red reactions described, namely the local reddening and the flare, are due to distinct causes. The colour of the flare at once suggests that it is produced by a dilatation of arterioles. The idea that it is due to a distinct mechanism and is the result of arteriolar dilatation is proved by further observation. If a subject is chosen, in whom both the flare to heavy stroking and the white reaction to light stroking are readily obtainable, the effect of the latter on the former may be tested. When a red line surrounded by a scarlet flare has been elicited, a light stroke is made at right angles across the first ; soon a white reaction appears, and the white band, as it becomes manifest, obliterates the flare but leaves the red line unchanged (*51*). In the white reaction, as we have seen, all the minute vessels contract ; by contracting in the circumstances of the present experiment they overcome the passive dilatation produced by the opening of the arterioles ; their active local dilatation remains undisturbed.

The flare fails to appear if the main vessels of the limb have previously been occluded,* it does not appear if adrenalin is injected immediately beneath the skin beforehand ; the local red line comes in both these circumstances, and, because the flare is prevented, the local reaction may appear all the more distinctly on that account. Of the two reactions, the local red line is independent of a forward movement of blood from the arteries, the flare is not.

To display the flare most widely and most clearly, the veins of the arm should be congested previously and so maintained until the arm is cyanosed. It then appears vividly red on a purple background. Moreover, if this method is used, it is found that the flare occurs more frequently and with lighter stroking than would otherwise be suspected. When, in relatively insensitive skins, it is seemingly absent, some degree of surrounding arteriolar dilatation is usually to be displayed by first rendering the arm cyanotic.

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* A very faint ghostlike flush or stain occasionally seen on the skin for a distance around the part stimulated has been thought to be due to active involvement of minute vessels (*214*). Although this is possible, it is certain that an active change in the minute vessels can play no more than a minor part in the flare as we see it on skin to which the blood flows freely (see page 220).

A flare that is at all bright is accompanied by a very appreciable rise of skin temperature ; this amounts usually to from 0·5 to 1·0°C, and when it is very bright the temperature of the warm arm may rise by 2·0° or more.

The evidence discussed clearly establishes that the flare originates in dilatation of arterioles, the precise order of which we may now proceed to discuss. In his account of the cutaneous vessels, Spalteholz (*231*) gives measurements indicating that the area of skin supplied by the last or terminal arterioles amounts to but a small fraction of a square millimetre. These arterioles spring from the subpapillary plexus, the meshes of which in the calf and gluteal region are named as each covering from 1 to 1·5 sq. mm.. These meshes are supplied by the arched and branching arterioles arising from the deeply lying cutaneous arterial network. If, for purposes of argument, we consider the arched arterioles diagrammatically and allow that each supplies (partly or completely) through its branches 2, 3 or 4 meshes of the subpapillary plexus in a vertical plane (as represented in Fig. 13), we arrive at an approximate idea of the area of skin surface that
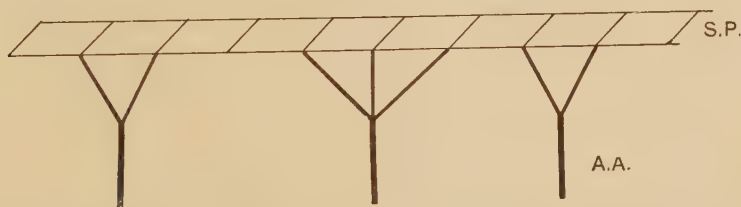
Fig. 13. A diagrammatic representation of the subpapillary arteriolar plexus (S.P.), the arched arterioles (A.A.) and their branches that supply it.

a single arched arteriole supplies. If such an arteriole dilates, it will be responsible for a quite distinct red spot in the skin, the edges of which will no doubt be diffuse, since the central part of its territory will be more adequately supplied than the periphery. The area covered will measure a few millimetres, more or less, across.

The marginal crenations of the flare measure a few millimetres. The small red spots, presented by the fading flare, presumably represent the centres of small arteriolar territories, for they recur with much precision in repeated flares (see page 201) ; the centres of these spots lie usually 3 or 4 mm. apart.*

A comparison of these and the anatomical measurements definitely points to the arched arterioles, uniting the cutaneous and subpapillary arterial plexuses, as the most peripheral that dilate. These arched arterioles are the smallest vessels in the skin that possess a strong muscular coat.

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* These observations were actually carried out, not upon the flare in response to stroking, but in the identical flare that appears, as we shall see, in response to histamine.

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Thus, allowing the details of the present argument to be valid, I have arrived at the conclusion that the flare is due to opening up of the last strongly muscular or *strong arterioles* (see page 3) of the skin (*161*). Very possibly it also involves arterioles of larger calibre.

The arteriolar flare differs from the local response in that it is dependent upon the integrity of the cutaneous nerves, a matter more fully considered in Chapter V. It differs from it also in that it is unobtainable over the surfaces of the viscera (*75*) ; the flare is peculiar to superficial structures such as the skin and conjunctiva.

In describing the local red line, evidence to show that the blood flow is increased in this reaction has been put forward. In the normal skin, heavily stroked, the local red line is set in a field of vasodilatation, for which the arterioles are responsible ; with lighter stroking this arteriolar flare may only become manifest, if it is present, when the arm is congested. It will be clear that the increased blood flow previously evidenced in the red line might conceivably be due to an associated but ill manifested flare. This explanation is insufficient, for the local reaction still appears red upon the purple background of congested skin, when the flare has been wholly abolished by nerve section and degeneration ; any opening up of arterioles of larger calibre than the terminal ones as a part of the local reaction, such as is discussed on page 41 must be a direct reaction, therefore.

Summary.

In the present chapter certain facts have been established and certain methods described. As these will form the basis of further discussion and experiments it may be wise to summarise and emphasise them.

Though as yet it has been considered in part only, we have seen already that the vascular reaction to firm stroking is complex ; it has been shown to consist of :—

(*a*) a local response, due to active dilatation of the minute vessels of the skin, including the terminal arterioles, the capillaries and the minute venules. This reaction is strictly confined to the line of pressure.

(*b*) a diffuse response caused by relaxation of the strong arterioles ; this response floods the field of the local response and spreads beyond it for varying and sometimes considerable distances.

These two responses are in all probability invariable reactions of the normal skin to *firm* strokes, though they are combined in different skins in varying proportions. The first occurs alone in response to lighter strokes, or the second is here so slight as to be indistinct ; the visible differences in the total skin reaction are essentially quantitative rather than qualitative.

It may be well, in terminating this chapter, to draw particular attention to two simple but most useful tests.

1. An active change in the tone of the minute vessels may be identified if, before it appears, the circulation to the skin concerned can be arrested by a high pneumatic pressure (200-300 mm. Hg), leaving in the skin a normal or slightly excessive quantity of blood ; for the corresponding change in the depth of skin colour will in these circumstances manifest itself fully when the change in tone comes. I shall in future term this test the **occlusion test.**

2. An increased blood flow to the skin, such as occurs particularly when the strong arterioles dilate, is distinguished by any means that ordinarily render the skin cyanotic ; in such circumstances the skin will remain red so long as the arterioles supplying it remain dilated. The customary test employed to detect increased blood flow, and it is the most delicate we possess for this purpose, is to impose on the veins a congesting pressure. As a routine I use 70 mm. Hg pressure, maintained for 3 minutes. This routine test I shall in future term the **congestion test.**

CHAPTER IV.

LOCAL ŒDEMA AND VARIOUS MEANS OF PRODUCING
THE TRIPLE RESPONSE.

In the last chapter, firm strokes were shown to produce a twofold reaction, dilating the minute vessels locally, dilating the strong arterioles over a greater area of skin. These effects may form the whole visible reaction. Often they are followed by swelling of the skin, a local œdema popularly termed a wheal (Figs. 15 and 16, page 49), or urticaria because it is associated with itching.

The skin of certain people is peculiarly susceptible to stroking, and whealing in these is called "factitious urticaria." This form of "dermato-graphism" has long been known in patients, has been regarded generally as pathological, and has been associated, unguardedly and erroneously, with distinct diseases too numerous to name (*11*, *196*). The passage from what is physiological to what is pathological is often insensible ; the present instance strikingly exemplifies the fact. Amongst young and perfectly healthy people whealing of skin as a sequel to firm stroking is by no means infrequent ; a detectable swelling is found in about a fourth of those tested and in about 5 per cent. a conspicuous wheal is produced (*159*). A little whealing in response to stroking is frequent, if not the rule, in children (*11*). The full reaction to stroking is certainly not pathological in the sense that it presents a qualitative difference ; such difference as exists is purely quantitative. A wheal may be produced on the skin of the back of almost any normal subject * by repeatedly stroking it ; six or ten firm strokes accurately superimposed usually suffice. The wheal customarily raised by the lash of a whip is an example of a single strong stimulus ; continued and hard friction of the normal skin wheals or blisters it.

The swelling that follows a single firm stroke on sensitive skin, and this is the most convenient for observation since upon it the wheal is produced easily and constantly, usually begins to appear in 1 to 3 minutes, and is generally at its height in 3 to 5 minutes. It is at first red and is surrounded by the flare previously described. It may project 1 or 2 millimetres or a little more above the general skin surface ; an exceptional case in which the skin is said to have lifted 6 millimetres was observed by Chatelain (*47*).† Shortly

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* The skin of horses often wheals to slight mechanical stimuli (*11*).

† Such is the measure given, though it seems to be overstated.

it pales, often conspicuously, the pallor being due in part, if not mainly, to the pressure exerted by transuding fluid upon the minute vessels. At first its margins are crisp and mark out precisely the borders of the local band of skin redness that precedes it. As time passes, the margins of the wheal become less sharply defined, since the contained fluid, being under pressure, tends to force its way gradually into the surrounding skin. Thus, the wheal grows a little in breadth, loses crispness and height ; gradually it subsides and disappears. It may remain distinct for one or many hours.

Repeated stroking of one area in susceptible skins does not in my experience add greatly to the reaction, nor alter its character.*

The full reaction to stroking, namely, the local vasodilatation, the flare and eventually local œdema, constitutes what I shall henceforth call the **triple response.**

It is by no means peculiar to this form of skin stimulation. Thus, blows, cuts or lacerations may be mentioned† ; but more important, because they are easily applied as tests to small and defined areas of skin, without materially inconveniencing the subject, are the prick and the scratch. Similar acute reactions are called forth by cold, freezing, burning, the galvanic and faradic currents, and by the application of one of a large number of irritant substances. Before further examining and discussing the mechanism of the full reaction, it will be convenient briefly to describe and compare the effects of a selected series of different stimuli.

Physical agencies.

The prick. If a sharp needle is stabbed into the skin with sufficient force just to penetrate the outer layers, but not to draw blood, this minute injury is soon followed by the appearance of a distinct though faint surrounding flare. This suffusion of the skin is arterial red in colour, it is irregularly circular in form, and dwindles in intensity at its edges, being usually about a centimetre, more or less, in diameter. This flare, soon becoming a little speckled, is accompanied by a distinct and detectable rise of skin temperature (0·2° to 1°C) ; it stands out brightly upon an area previously rendered cyanosed in the congestion test ; it is abolished or rendered indistinct by superimposing upon it the white reaction, produced by gentle stroking (*51*). Thus it resembles the flare that surrounds a heavy or repeated stroke in all particulars, except that it is less both in intensity and distribution. On the normal and uninfluenced skin this flare may seem to be the complete vascular reaction but, if the area is first congested a little and the circulation is then brought to a standstill (the occlusion test), no flare is seen to follow pricking ; in its place there appears a small and faint purple spot immediately surrounding the puncture, and representing the local vasodilatation.

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* In a curious case recorded by Renaut (*216*) lesions ending in necrosis are recorded, but it is not clear that these resulted simply from a single mechanical stimulus.

† In one exceptional case of mine, the reaction occurred to stretching of the skin ; in this case a stroke with a small blunt point gave wheals 23 mm. in diameter.

Fig. 14. (× $\frac{4}{5}$). *Development of the triple response.* The back of an
          urticarial subject has been firmly stroked and at the same time a
          single histamine puncture has been laid down. The photograph,
          taken 1½ minutes after stimulation, shows the dark red line of the
          stroke and a diffuse surrounding flare ; the needle prick likewise is
          surrounded by a flare. No wheals have appeared as yet.

Fig. 15. The same skin at the end of 3½ minutes. The flares surrounding
          the two stimuli are now brighter and more sharply defined and wheal-
          ing has nearly reached its full height.

Fig. 16. The same skin at the end of 40 minutes. The lighting has been
          altered to display the wheals more fully. The wheals are pale, they
          have widened, and their edges are less sharply defined. The flares
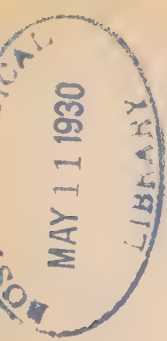   have subsided.

Fig. 14.

Fig. 15.

Fig. 16.

A prick with a needle ultimately calls forth a circular wheal on susceptible skins, a minute wheal on the skins of most young people ; repeated pricks over a small area evoke a very distinct wheal in the less susceptible, as Ebbecke has stated (*75*).

The scratch. If the needle point is drawn firmly over the skin with force just insufficient to break the surface of the living skin, a comparable reaction appears. A flare of arterial colour soon develops and extends a centimetre, more or less, on either side of the line scratched. The borders of this flare are broadly parallel though somewhat irregular ; the flare fades away at its margins and at a later stage is speckled. It appears brilliantly red in the congestion test ; it is accompanied by rise of temperature (0·5° to 2°C) ; it is abolished by a superimposed white reaction, and fails to appear if previously the circulation to the skin has been arrested. In the last circumstance, however, the line of scratch is marked by a narrow dull red or purple line. As in the case of stroking or of the pin prick, the vascular reaction is twofold, consisting of a local and a diffuse response.

It is followed by a fine linear wheal. The scratch of a cat's paw or of a thorn usually wheals a child's skin.

Freezing. The effects of temperatures, sufficiently low to freeze the skin, may be studied by one of several methods. The skin may be frozen by spraying it with a highly volatile fluid such as ethyl chloride, or by pressing on to it a solid stick of carbon dioxide snow. It may be frozen by applying it to cold metals. All these methods yield substantially the same results, though these vary according to the lowness of the temperature employed and the length of its application. In hard freezing with ethyl chloride, temperatures as low as -25°C, with solid CO_2 much lower temperatures, may be obtained ; the reactions in the last case may be severe and the skin destroyed.

Love and I (*171*) used for the most part a special device. A square bar of copper $1\frac{1}{2}$ cm. broad and 30 cm. long is bent to a right angle (Fig. 17). The long arm is immersed in acetone to which solid carbon dioxide is added in quantities sufficient to reduce the temperature to a desired point. The other end of the bar, cut square, has a very thin and flattened constantan wire soldered to its centre, the rest of the wire being insulated. This centre point serves as one thermo-electric junction, which, being connected to a second at constant temperature and to a mirror galvanometer (as in Fig. 8, page 15), registers on calibration the surface temperature of the end of the copper bar. This end of the bar is placed gently against the surface of the skin of the arm and is maintained there until the skin freezes.

Using this simple apparatus, it is found that the skin can be frozen at temperatures as high as -2·2°C, and freezing to varying depths or hardness can be obtained by changing the temperature and the duration of freezing. The instant at which freezing begins is accurately indicated by a pricking sensation in the skin, identical with that produced by a weak galvanic

current. According to the degree of frost required, freezing is allowed to continue for from 5 to 10 seconds (temp. of about -20° to -15°C) or from 45 to 60 seconds when higher temperatures are used (-10°C to -5°C). On removing the contact the pricking sensation at once ceases, and a square area of frozen skin is seen ; it may be picked up in the fingers and varies in thickness and in hardness.
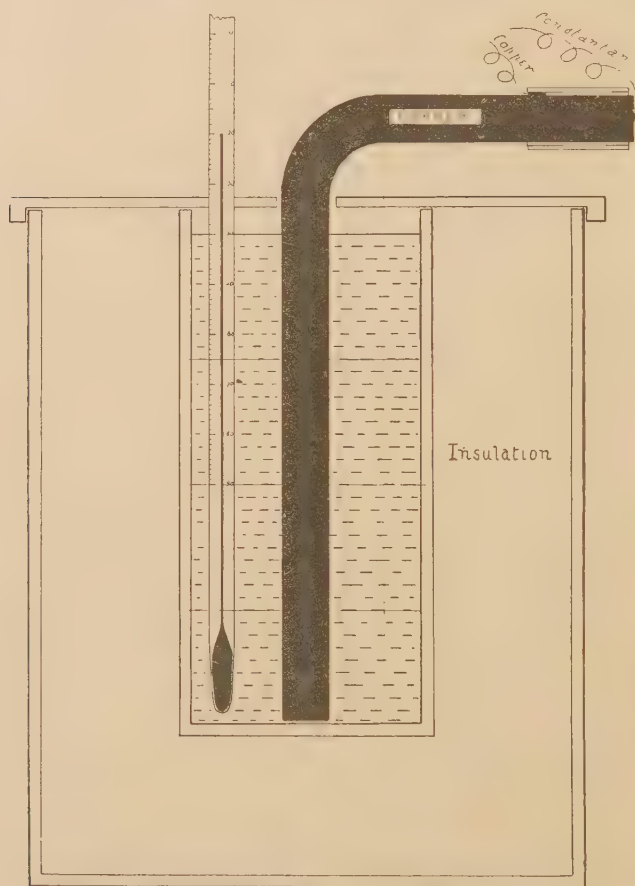
Fig. 17. An apparatus (× 2/5) used for cooling the skin to, or freezing at, known temperatures.

When the skin is frozen hard and throughout, the subsequent events are as follows. The sharply defined frozen area is yellowish white or white, according to the hardness of freezing, and is a little raised ; it soon thaws. The skin around becomes suffused with colour over a considerable area about 35 to 45 seconds after freezing has begun and is soon warmer than normal (0·5 to 1·5°C). When thawing is complete (in half a minute or more) the central area is still paler than the surrounding skin, but suffuses deeply with colour as blood runs into it from its margins, which thaw first. At about $1\frac{1}{2}$ to 2 minutes the surrounding flare begins to diminish in extent, it becomes

more sharply defined and, if freezing has been severe, speckled. Fading of the flare continues until the skin originally frozen stands sharply outlined as a bright red area. The flare in light freezing lasts about 3 minutes. The local reddening appears, but appears alone, if the skin is frozen and thawed during an occlusion test. The flare appears brilliantly red in the congestion test.
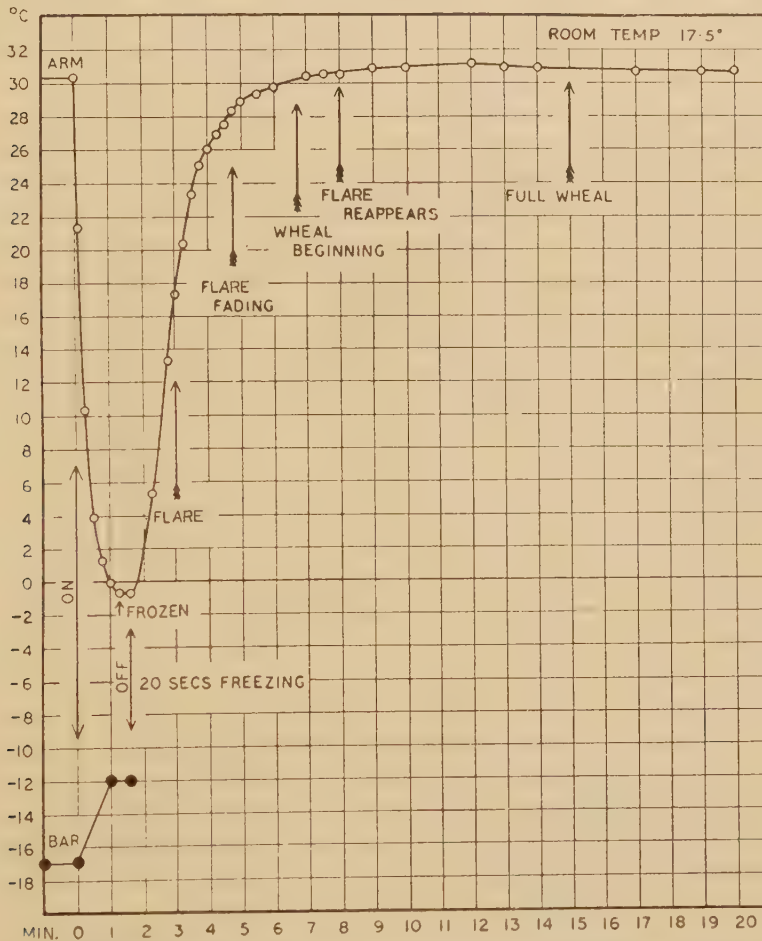
Fig. 18. A chart showing the effect on subdermal temperature of applying a cold bar of copper to the skin. The subdermal temperature is charted above, and the surface temperature of the bar below. The skin froze, and the times at which the surrounding flare and the wheal appeared are marked on the curve.

In from 3 to 6 minutes from the stage of thawing, itching is felt and the central skin begins to swell. A square wheal, sharply cut at its edges, forms and remains for one, several, or many hours, gradually subsiding (Fig. 18). It leaves behind it an area of red skin, which for several or many days marks out the area frozen.

The essential features of the reaction are a long lasting dilatation of the minute vessels locally, a transient and widespread arteriolar flare and, finally, local œdema. In other words the reaction to freezing conforms to the usual type in every particular.

It is the rule that neither persistent reddening nor whealing occurs unless the skin has actually frozen ; whealing does not usually follow light or superficial freezing ; it always follows hard freezing and continues to the formation of blisters if freezing has been severe. Subsequent scaling of the skin locally is usual and after severe freezing the skin becomes pigmented, phenomena common to many forms of injury of the epidermis.

The reaction as a whole is due to injury arising out of the solidification of the tissues ; as will be seen later, the effect of cold plays little or no part in it.

A consideration of the effects of freezing at different temperatures and for different periods of time, and a comparison with the states of solidification that result, lead to the belief that the severity of the after-effects is controlled by two chief factors, namely, the hardness of freezing and the depth to which it penetrates. The hardening up and firm union of crystals, at first separate, is an event especially calculated to produce cellular damage. In the case of red blood cells, it is well known to liberate the contents of the corpuscles. A greater depth of freezing is equivalent to the involvement of more cells in the injury.

Whealing of the skin with mild grades of frost, blistering with more severe grades, is well known to those who employ freezing in the treatment of small skin lesions (*181*). If freezing is still more severe or long continued, the vessels subsequently thrombose, the tissues become necrosed and are detached. Thrombosis is unessential to the lesser reactions ; in these, when the wheal has subsided, the blood may be expressed from the reddened skin that remains.

The reaction to freezing discloses a phenomenon that in the instance of most tissue injuries escapes notice. Because, after freezing and thawing, the tissues are cold for some while subsequently, whealing occurs comparatively slowly (see page 92) ; by the time it starts the surrounding flare may have faded away ; in these circumstances it is frequent to observe that the flare reappears while the wheal is growing. The same phenomenon is sometimes suspected to occur when a wheal follows stroking of a susceptible skin but, as the original flare and wheal are in this case more nearly contemporary, the appearance of a second flare, or an exaggeration of the original one, is less easy to recognise. This *secondary flare*, as Love and I (*171*) have called it, we have ascribed to the mechanical damage arising from the exudation of fluid into the tissues.*

* From this observation it would appear that the exudation occurs, in this form of injury at least, with a rapidity tending to be inimical to the tissues. That being the case, any means that would prevent whealing or lessen it, should prove beneficial. Arresting the circulation, or greatly slowing it, for 15 minutes, thus covering the period of thawing, has this effect ; it is found to diminish subsequent whealing and to expedite the rate at which the whole reaction subsides. We therefore recommend that this method should be tried in treating frostbite and also burns of the limbs, the latter when seen in a stage before blisters have developed.

Supercooling. When a cold bar is applied to the skin, especially if this skin is unmoistened and contains much of its natural grease, often the temperature may be reduced far below the freezing point of skin, without the tissues solidifying. The freezing point of skin cannot be far removed from -0·6°C, which is that of 1 per cent. salt solution. Yet the surface temperature of the skin may be lowered on occasion as far as -20°C and the subcutaneous temperature may fall simultaneously to -9°C, and there be maintained for a long while, without there being a trace of freezing (Fig. 19).
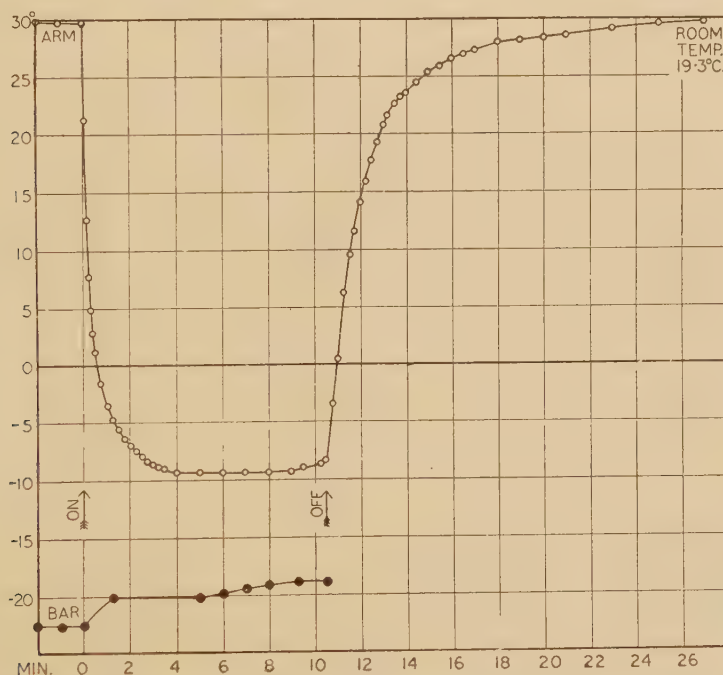
Fig. 19. Chart showing the change in subdermal temperature when the skin is brought into contact with a cold bar of copper. The subdermal temperatures are charted above, those of the surface of the bar below. To illustrate supercooling of the skin.

The phenomenon of supercooling is well known in the case of fluids, and the factors that govern it are not easy to control. The extraordinary capacity of skin to supercool (*171*), must often save it from freezing and from consequent damage, when it is exposed to atmospheric temperatures of -10° to -30°C.

It is the rule that supercooling, even if continued, is followed by neither persistent reddening nor whealing ; on occasion however, especially if the temperature has been very low and long lasting, subsequent whealing occurs, although the most careful previous examination has failed to discover a trace of frost in the skin. This whealing is accompanied by the usual flare and, when it subsides, leaves behind it an area of local vasodilatation.

Certain skins are particularly susceptible to injury by cold itself, a matter requiring further investigation. In most subjects a temperature of -5° or -10°C, even if long maintained fails to damage ; but Blachez (*24*), Fraser (*88*) and Duke (*72*) have reported instances in which contact with cold objects, immersion of the skin in cold water for a few minutes, or walking in wind on a rather cold day has been followed always by erythema, itching and conspicuous whealing of the exposed area. In Duke's case immersion of the skin in water at 10° to 15°C for 2 minutes formed an adequate stimulus. In Blachez's case the mucous membrane of the throat appears to have been similarly sensitive.

The burn. If a test tube of scalding water is brought into momentary contact with the skin, a smarting pain is felt. A single contact of the kind
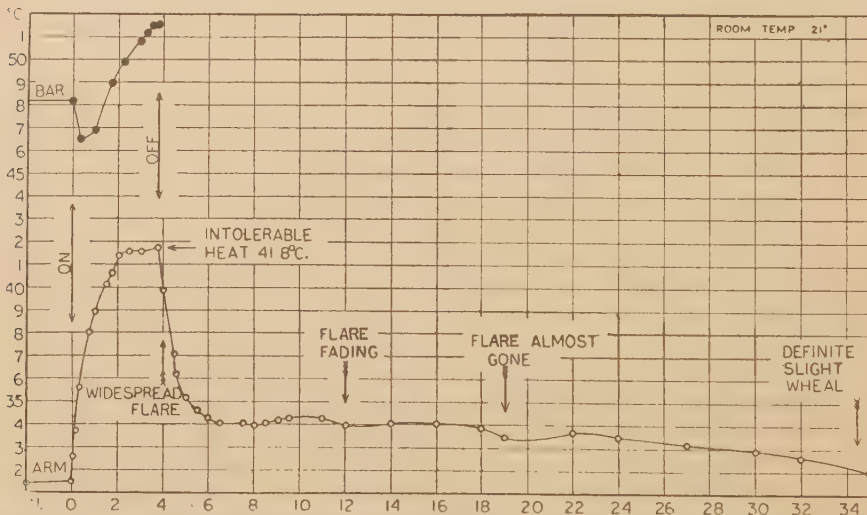
Fig. 20. A chart showing the effect upon subdermal temperature of bringing a hot copper bar, the temperature of which is subsequently raised a little, against the skin. Illustrating experiments in which the intolerable point was tested, and giving the time relations of the visible skin reaction.

is soon marked by a red spot on the skin. One or more contacts of the test tube produce also a widespread flare, which may reach many centi-metres in diameter. The flare has the characters now repeatedly described, a bright colour, an irregular edge becoming speckled in fading and so forth, the skin being hotter than the pale skin beyond (*164*). These phenomena and the vivid redness of the flare in a congestion test, proclaim it again to be arteriolar in origin. Thus burning heat also calls forth the two-fold vascular reaction previously described ; it causes œdema too.

Momentary contact with a cautery produces after a time a local blister, which is an advance upon the wheal. When a wheal is examined histolo-

gically, an intimate œdema of the true skin is found (Gilchrist *93*, and Hodara *117*), the fluid is not free. In the blister the fluid is in excess, breaks down small barriers, and comes to form a pool within the superficial layers of the skin. If the skin is heated almost to the intolerable point and this state is maintained, simple whealing follows and this may or may not continue to a blister. A person falls asleep before a fire and the amount of heat to which the shins are exposed may induce insufficient pain to waken him ; yet sometimes this long lasting stimulus suffices to raise wheals or even large blisters on the skin.
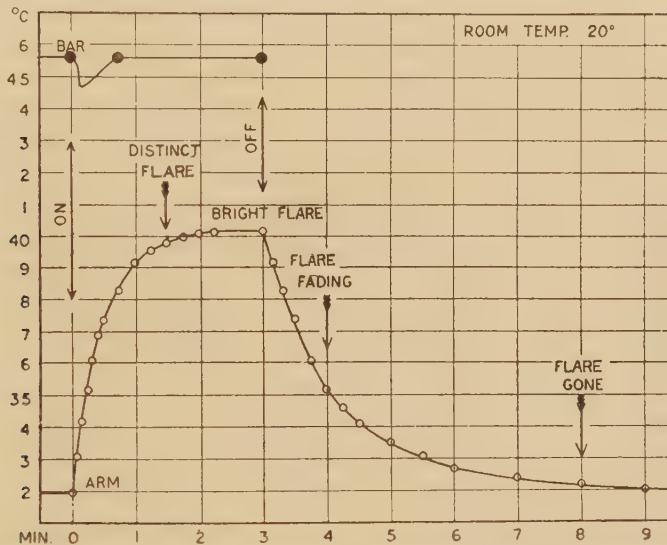
Fig. 21. A chart showing the effect of applying a hot copper bar to the skin, upon subdermal temperature. Illustrating experiments in which the minimal temperatures required to produce a surrounding flare was estimated.

Using the bar previously described (Fig. 17, page 52), heating one end of it, and applying the other at a known temperature to the skin, Love and I (*171*) investigated the temperatures actually required to produce the signs of tissue injury. The highest temperature that can be tolerated for more than a few seconds lies between 47° and 48·5°C. If a lesser heat is applied and this is gradually raised, it becomes intolerable when it reaches points lying between 51·5° to 52·5°C (Fig. 20). These are surface temperatures the intolerable point when tested by means of a thermo-electric junction placed subcutaneously, lies around 42° to 43°C. All these temperatures are injurious. A surrounding flare is produced when the surface temperature is raised to 43° or 44°C ; * and the subcutaneous temperature to from

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* Immersion in water at these temperatures fails to produce a flare in the adjacent unimmersed skin. That is so because the skin temperature does not rise quite to that of the water ; the arm becomes jacketted by a cooler layer of water.

37° to 40°C (Fig. 21).   The application of heat that is just short of the intolerable point wheals or blisters the skin if it is maintained.

Electrical currents.   A battery of 2 to 4 volts is connected to two electrodes, the anode consisting of a large flat contact, the kathode of a fine sewing needle.   The needle is supported by driving it through a flat cork, the point just emerging.   The two electrodes are laid on the arm, the needle point touching, but not penetrating, the skin.   A few seconds after the circuit is made, pricking is felt around the needle point, it increases in intensity and may become burning in character.   A meter in the circuit at first shows the passage of a very minute current ; this rises during the experiment and reaches 50 to 200 microamperes at the end of about 15 seconds.   The current is now broken and the cork lifted.

On close examination a minute circular patch of shiny and slightly discoloured skin is seen.   Within a minute, a little more or less, the spot is surrounded by a bright flare, several centimetres in diameter ; it has the usual arteriolar character and soon subsides ; it shows up red in a congestion test and is accompanied by increased warmth.   The purely local vascular reaction tends to be obscured by the little central lesion, but is distinctly to be observed in occlusion tests.   Shortly swelling appears locally and a little circular wheal grows until it is 4 to 6 mm. in diameter.

The method described is that of Ebbecke (*79*) and, as he states, whealing follows only when the needle point is the kathode, never when it is the anode. He explains the reaction on the basis of a simple stimulation of the living epidermal cells ; an interpretation with which I am unable to agree.   The experiment is a diminutive electrolysis experiment (*176*) ; the current liberates minute bubbles of hydrogen in the skin ; these may be seen by watching the skin microscopically.   These bubbles disrupt the horny layer of the skin and thus produce the little shiny discoloured patch upon the skin. Ebbecke's views are further discussed in a footnote to page 83.

The more extensive thrombotic and destructive effects of stronger electrolysis of the skin, and the associated inflammatory reaction, form the basis of a widely used remedy for small skin lesions, such as nævi.

The application of *faradic* currents, as strong as may be tolerated for 10 seconds, produces a local reddening and a surrounding flare of the usual type.   Whealing usually follows if such a current is maintained for $\frac{1}{2}$ to 1 minute.

Irritant substances.

There are many familiar substances, such as corrosive acids, caustics, preparations of mustard, cayenne pepper or cantharides, which when applied to the unbroken skin produce redness and ultimately whealing or blistering. To place such substances on the skin and to study the reactions that they yield is often either inconvenient or insufficient for the purposes of enquiry.

The nature of the various substances differs much, they penetrate to the living cells after varying and often long intervals of time ; it is impossible to compare at all satisfactorily the time relations of the various phenomena that appear in these circumstances. In surface applications relatively large doses must be applied to secure an effect ; moreover the substance continues to penetrate for an unknown time after the reaction begins, and maintains the reaction or increases it beyond the desired point. The application of substances to unbroken skin presents, as does application to a scarified skin, a further and material disadvantage, in that the amount of skin used up in repeated tests soon becomes too considerable.

The most precise and convenient method of studying most of the substances named is by pricking them into the skin (*164*). Preferably a solution of known concentration, the solvent itself inert, and usually normal saline, is used and a small drop is placed on the skin. Through this drop, a needle point is driven and the drop of fluid is at once removed. To describe the action of all substances known to produce whealing of the skin is unnecessary ; to illustrate will suffice. I take histamine as a type.

Histamine. Histamine or β-iminazolylethylamine is the amine produced when carbon dioxide is split off from histidine, a substance occurring naturally in the body and a protein derivative. It has been extracted from the mucous membrane of the gut by Barger and Dale (*10*) and recently from the liver and lung (*20*). A similar or identical base has been isolated from ergot, and it has been prepared synthetically.

The reaction to histamine, first reported by Eppinger (*81*), and further explored by Sollman and Pilcher (*229*), has been fully described by Grant and myself (*164*). This base is made up in normal salt solution in a concentration of 1 in 3,000,* using the phosphate (1 in 1,000), and is pricked into the skin. The reaction, which begins in about 20 seconds, consists of a central and local reddening, best displayed in an arm to which the circulation has been arrested. It is then circular, sharply defined, and has ultimately a diameter of about 3 to 4 millimetres (Fig. 12, page 39). On an arm in which the circulation is undisturbed, it is never so distinct, being masked by the accompanying flare (Figs. 14 and 15, page 49). This flare has the precise characters previously described and behaves similarly to tests ; speckling as it fades is often particularly distinct. The flare has a usual diameter of 2, 3 or more centimetres ; soon after its appearance the central area begins to swell, and a discrete wheal 3 to 4 or more millimetres in diameter forms ; this is generally at its height in 3 to 5 minutes, when it becomes pale (Fig. 22,

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* The concentration stated here and subsequently is calculated in terms of the base. The phosphate has a molecular weight approximately thrice that of the base. A 1 in 300 solution, occasionally used, has a P$_H$ of 4·9 ; a solution of acid potassium phosphate of equal acidity has no effect when pricked into the skin, but preferably a solution of histamine of this or greater strength should be neutralised before it is used.

Fig. 22.   (× 7/8).   *Nettle sting and histamine reactions*.   A small piece of
        nettle leaf, carrying 2 hairs, was brought in contact with the skin of
        the forearm and a sharp burning pain was felt ; immediately a
        histamine puncture (1 in 3,000) is made a little distance away.
        A flare soon surrounded each stimulated point, and wheals began to
        develop at the sites of puncture. The photograph was taken at the
        tenth minute.

Fig. 23.   (× 11/12).   *Method of comparing substances that wheal the skin*.   A
        suitable number of squares is marked out on the skin and, in the
        centres of these, drops of the fluids to be tested are placed ; three or
        four drops of each fluid are arranged in corresponding rows, and the
        nature of the fluids indicated by writing on the skin at the side.
        The skin is now quickly punctured through each drop of fluid, a clean
        needle being used for each row. The wheals are compared when they
        have developed fully. In the present example the wheals produced
        by 4 punctures through hydrochloric acid (5 per cent.), through
        caustic soda (5 per cent.), through histamine (1 in 3,000) and through
        saline (the diluent of the remaining reagents) are shown 7 minutes
        after puncturing the skin. The wheals produced by acids and alkalies
        are equal, those produced by histamine are very slightly larger.
        Very slight swelling occurred over the sites of puncture through normal
        saline, but in only one instance was this swelling sufficient to appear
        in the photograph ; this, the last stab, was stated by the subject to
        have been more forcible than the remainder.

Fig. 24.   (× 17/20).   *The white halo*.   Histamine (1 in 300) has been pricked
        into the arm and has whealed the skin. The reaction 5 minutes after
        puncture is shown, the wheal presenting two small radiating projec-
        tions.   The flare has subsided, becoming smaller, more sharply
        defined and speckled ; in receding it has left a zone of circum-
        ferential pallor and this pale zone is invading and is breaking up the
        remainder of the flare.
                This figure is described on page 200.

Fig. 22.

Fig. 23.

Fig. 24.

page 61); after a while its edges lose their initial crispness, and the wheal slowly subsides, disappearing entirely in the space of about an hour.

Other irritant substances. The earliest reference to whealing of the skin by poisonous substances introduced into it appears to be that of Phillipson (*204*), lists of such bodies will be found in the papers of Sollman and Pilcher (*229*) and of Török and Hari (*247*). Those that I have tested personally and that have produced acute whealing when pricked into the skin are summed up in the following table. This list of irritant substances is by no means exhaustive.

Substance.	Strength.	Compared with histamine.
Hydrochloric acid	1 in 20	
Lactic acid	1 in 5	Wheals smaller.
Formic acid	1 in 5	Wheals sometimes smaller.
Formaldehyde	1 in 10	
Caustic soda	1 in 20	
Silver nitrate	1 in 12	Wheals smaller and subsequently form minute pustules.
Copper sulphate...	1 in 10 ⎫	Wheals formed more slowly (about $\frac{1}{2}$ usual rate).
Mercury bichloride	1 in 18 ⎭	
Iodine	1 in 20	Wheals smaller and develop somewhat more slowly.
Morphine hydrochloride	1 in 100	
Atropine sulphate	1 in 50	
Chloroform	Concentr.	
Mustard oil	Concentr.	Wheals smaller, flush in greater evidence.
Cantharadin in acetone	1 in 20	Wheals smaller, blister later.
Nettle sting*	Natural	
Flea and gnat bites in the susceptible	Natural	
Fairchild's peptone†	1 in 10	Wheals smaller.
Alcoholic extract's of liver, lung and skin (see 20 and page 235 also)	Active substance very dilute	
Fish extract in a susceptible subject ...	Extremely dilute	Wheals are perhaps slower in development.

Calcium chloride (1 in 10) urea (saturated solution), both stated to wheal by Sollman and Pilcher, have given consistently negative results by our method. Absolute alcohol and acetone give no whealing. Pepsin 10%, chloral 1 in 5 of alcohol, sodium salicylate 1 in 50, have shown either very slight whealing or have been without distinguishable effect.

* The nature of this poison is discussed by Haberlandt (*101*).

† Professor A. J. Clark prepared for me the following solutions :—

Five grammes of Fairchild's peptone were dissolved in 50 c.c. of water ; of this :—

A. 25 c.c. were dialysed for 5 days at 0°C without pressure.

B. 25 c.c. were precipitated with alcohol and ether and

    (a) precipitate taken up in 25 c.c. of water ;

    (b) ether soluble fraction taken up in 25 c.c. of water.

The three solutions A, Ba and Bb all yielded small but distinct wheals when pricked into the skin and there was little to chose between their potency in this respect, A being slightly the weakest.

Of the substances named some require emphasis.   Thus, it is to be noted particularly that solutions of acids and of alkalis of suitable strength produce identical reactions.   These and most of the remaining substances do not find their way into the skin in natural circumstances.   Poisons that most skins occasionally experience are those introduced by bites or stings of parasites or insects, or by the stings of poisonous plants.   Extract of fish illustrates one of a very large group of poisons, of which pollen, strawberry juice, egg yolk are other examples, in which the reaction is confined to those peculiarly susceptible ;   this particular example will be commented upon later at greater length (page 113).

The reaction times of all these substances have been compared by pricking each into the skin* simultaneously with a histamine solution (1 in 3,000) ; the extent of the reaction has been compared with that yielded by the last and each has been controlled by simultaneously puncturing the skin with normal saline or other solvent.   When no remarks are entered in the appropriate column of the preceding table it is to be inferred that the reaction called forth by the substance cannot be differentiated either in its type, in its degree, or in its time relations from that of histamine in the strength mentioned. Each and all yield a local redness, a surrounding flare and finally a local wheal, and the appropriate tests have shown in each case that the local redness is due to primary dilatation of the minute vessels, and the flare to dilatation of strong arterioles.

A comparison of the reactions as a whole.

The reactions of the skin to mechanical injuries of different kinds, to excessive heat and freezing, to galvanism, faradism, and to a variety of poisonous substances, have been set forth deliberately in detail so that they may be compared accurately.   They are all fundamentally alike ; at the site of stimulation each produces a local change, due to a primary and active dilatation of the minute vessels ; each is followed by a widespread flare due to the opening up of strong arterioles ; each causes œdema of the skin. This triple response, however produced, is constant in all essential particulars. To emphasise the fact, to illustrate the time relations, and especially to link together the effects of physical damage and chemical poisoning, the following example is cited from a paper by Grant and myself (*164*).   The skin of a subject known to wheal easily in response to mechanical stimuli was stroked and at the same instant histamine (1 in 3,000) was punctured into the skin. The following table presents the time relations of the two reactions (see also Figs. 14 to 16, page 49).   It will be seen how closely these correspond.

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* With the exception of the poisons introduced by bites.   Here I rely on observation of recent bites untimed.

Zero time.	Stroke.	Histamine punctures.
After 20 secs.	red line begins	red spot seen.
„ 30 secs.	flare begins	flare begins.
„ 1 min. 10 secs.	wheal begins	
„ 1 min. 20 secs.		wheal begins.
„ 3 mins.	wheal almost full and pink	wheal almost full and pink.
„ 8 mins.	wheal pale	wheal pale.
„ 47 mins.	wheal pale and diminishing	wheal pale and diminishing.

The farther the comparison is carried, and it has now been carried in many more directions than have yet been indicated in this chapter, the closer is the resemblance found to be. Similar agreement exists between other forms of stimulation. Thus, if a galvanic and a histamine stimulus, graded to give the same size of wheal, are laid down together, the subsequent events in the two areas proceed hand in hand with noteworthy precision. In this connection I show two illustrative photographs (Figs. 22 and 23, page 61); the first displays the equal progress of two reactions to the simultaneous stimuli of histamine puncture and nettle sting. The second compares the effects of acid, alkali, histamine and saline (the control), all punctured into the skin and as simultaneously as possible.

In minor details, for the most part readily explainable, the reactions may vary. Naturally they differ in distribution according to the area of the skin involved by the stimulus and the strength of this stimulus. They differ slightly on occasion in their time relations, though it is clear in many instances that such differences are theoretically unimportant. The first sign of reaction comes a little more quickly when the stimulus is powerful, though the variation is less than might be expected *a priori* ; thus, if histamine of 1 in 30, 1 in 300, 1 in 3,000 and 1 in 30,000 strength is used, the reactions to the first two lead slightly and in the last is a little delayed, but scarcely more than is to be accounted for by the fact that the stronger reaction is more conspicuous in its early stages and on this account is recognised earlier.[*]

Appropriate strengths for stimuli of different kinds may be chosen to give equal whealing ; when this is done the comparison becomes more exact and the greatest harmony is found. Burning heat is difficult to regulate to a sufficient nicety, although the times at which the flare and wheal appear in response to a single stimulus of the kind do not differ substantially from the remaining responses. But stimulation is apt to be carried too far in this instance, the reaction is more prolonged, and leads ultimately to visible loss

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[*] A stronger solution introduced remains longer in place or is able to diffuse farther and thus to involve fresh tissue ; a stronger solution therefore yields in general a wider and more lasting reaction ; especially does this statement apply to the flare.

of tissue and scarring. The same will of course follow if such a stimulus as freezing, galvanism or the application of a caustic substance is increased in its degree or its duration. When cold is applied it causes contraction of certain vessels and in this state they become frozen; but if due allowance is made for the time of thawing and for the subsequent opening of the affected and cooled vessels, then the times at which flare and wheal appear in this instance also correspond very closely to their appearance in the remaining reactions.
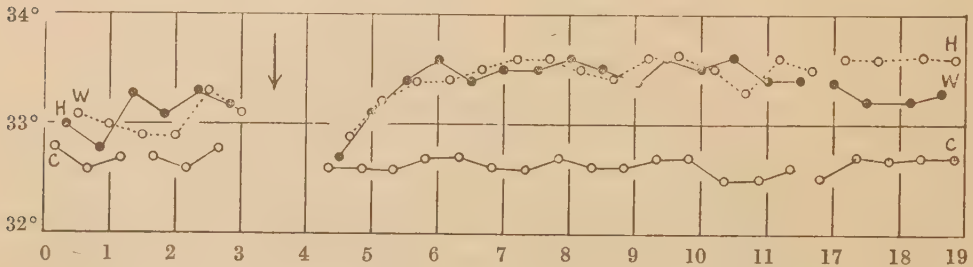

Fig. 25. To compare the reactions called forth by different stimuli, the thermo-electric couple has been used. Exploring the back of a susceptible subject the skin is searched to find two symmetrical areas of equal and constant temperature. One of these is now stroked, the other injured with three closely set histamine punctures (1 in 3,000), at the time marked by the arrow. Temperature readings, started before stimulation, are taken from three areas, namely, that stroked (W), that punctured (H), and a third or control area (C). As the accompanying chart shows, the temperature of the last remains constant throughout, that of the two stimulated areas rises simultaneously and a little more than 0·5°C to a plateau in each case. Time in minutes.

To sum up, it is clear that our type reaction or triple response, comprising as it does a local dilatation of the minute vessels, a widespread arteriolar dilatation, and finally whealing, may be brought about by a great variety of means. Mechanical, electrical, thermal, chemical stimuli all produce essentially the same responses of the vessels. To describe in detail the several reactions is largely to reiterate. This similarity of response is remarkable, as we have seen; it assumes greater significance when it is known that the three essential parts of the triple response are each independent of the other. The flare is called forth through nervous channels, the local dilatation and the œdema are not, but the two last are also separable. The evidence for these last statements is examined in the following chapter.

CHAPTER V.

MECHANISM OF THE FLARE AND OF THE WHEAL.

Influence of the nerves of the skin.

THE influence or lack of influence that the cutaneous nerves exert upon the red reactions described is of much interest and importance. Müller (*196*), in his early observations, cites an instance of anæsthetic skin, due to a peripheral nerve lesion, and finds that the flare around a pinprick or scratch fails to appear in this circumstance. In the same article he instances cases of paraplegia following caries of the spine or fracture of the spine and states that, while the flare in response to scratching is preserved in skin corresponding to segments of the cord above and below the area damaged, it is abolished over a narrow zone corresponding to the actual level of the cord lesion. He cites these cases and that of the peripheral nerve lesion, in support of his conclusion that the flare immediately surrounding the injury depends upon integrity of the spinal reflex arc. These observations of Müller, seemingly so clear, have influenced later writers (Krogh *137*, Ebbecke *75*, and others *212*) and have led them to accept a conclusion that in its application to the human skin is erroneous. A vasodilatation corresponding to that described by Lovén (*180*), namely, one due to an impulse that is propagated by stimulating a sensory nerve centrally and that is reflected from the spinal cord back to the area from which the stimulated nerve arises, is so far unknown in the case of the human skin. It is quite possible, if not probable, that it occurs, but such reflexes should be distinguished from that here described. There is a strong *a priori* reason for doubting the validity of the view that the latter is a spinal reflex. When the skin is pricked, a patch of skin precisely surrounding the point damaged becomes flushed, an area perhaps less than a square centimetre in extent ; when a long scratch is put down on the skin, the line of scratch and a narrow band on each side of it, and of almost uniform width, is involved. If the flare is a spinal cord reflex, then every square centimetre of the skin of the body would require its own particular representation in the cord before even approximately accurate reflection of the stimulus could occur. An explanation of the scratch flare, along the lines Müller suggests, seems from this argument alone to be untenable.

Ninian Bruce (*32*) showed, sixteen years ago, that the reddening and swelling that follow an application of mustard oil to the conjunctival sac are independent of the central nervous system, in that they occur after the

sensory nerves to the conjunctiva have been divided. He further stated that, if the nerves are cut and are subsequently allowed to degenerate, or if their endings are locally anæsthetised, the reaction is unobtainable. He concluded that the inflammation depends on a local reflex, the impulse travelling, according to his view, up one end branch of a sensory nerve, and down a second to a vessel. This form of reflex, for which he employed the term "axon-reflex" requires no interpolated nerve cell on its path. His observations have been in the main confirmed by Bardy (*9*). Bardy does not find the reaction to be completely abolished, but to be much lessened by nerve degeneration. It seems proved that the reaction of the conjunctiva to mustard oil is in chief part dependent upon a local reflex, and that the central nervous system is unconcerned in it.

It is easy enough to understand how a local reflex of the kind described by Bruce would limit the field of vasodilatation to the immediate neighbourhood of injury. It would surely be extraordinary to conclude that the reflex in the case of the conjunctiva is purely local, while a reaction that is similar, and exercises a similarly protective influence on the skin of the body, is called forth through long channels reaching to and from the spinal cord.

Grant and I (*164*) were the more discontented with the evidence for the spinal reflex since Breslauer (*28*) had shown that an erythema due to a local reflex follows the application of mustard oil to the skin itself. This oil, when painted on the normal skin, induces itching and burning pain, and Breslauer states quite emphatically that the accompanying flare occurs when the sensory nerve trunks to the skin are interrupted by section or anæsthesia, but that it is abolished once the nerves become degenerated or when the skin is itself anæsthetised by local injections of novocaine. The parallelism between Breslauer's observations and those on the conjunctiva is in this instance exact, and both are clearly due to a local nervous mechanism.

The reaction, as Müller (*196*) depicts it in his paraplegic patients, is not doubted, but from personal experience we can say that in cases of pressure paraplegia it is not invariable. The scratch may in such yield a uniform flare right through from normal to anæsthetic skin. When we enquire in more detail, we find that Müller assumes the break in the flare to be due to *cord* damage ; he does not exclude simultaneous damage to the posterior root ganglia or to the sensory nerves themselves, likely events and either of which would bring about degeneration of these nerves in course of time. In a case of paraplegia caused by the pressure of an aneurysm on the cord, recently examined (*167*), the flare to scratching appeared over the area of every spinal nerve. The 6th to 9th segments of the cord were compressed and destroyed, but the corresponding posterior root ganglia were intact. When we enquire as to the duration of the peripheral nerve lesion that Müller cites, the question of degeneration remains unanswered. Thus, those observations form indecisive evidence that the flare is a spinal reflex ; they are not in actual conflict with the view that it depends upon a purely local mechanism, to which the remaining evidence clearly points.

In the hope of carrying the question to a final decision, many observations have been made in my laboratory (*164, 167*). Material of several kinds has been used, and I describe the various available methods in some detail because they have different values.

Local anæsthesia. This method has been used by many (*28, 43, 164, 249, 251*). A 2 per cent. solution of novocaine is injected subdermally into skin areas of the forearm 2 to 4 cm. in diameter. The injections are not usually made intradermally ; such are of little value, because a wheal is formed by the injected fluid and the area becomes white owing to the collapse of the skin vessels under pressure. They are made just beneath the true skin and soon the skin area involved becomes red in colour and entirely insensitive to touch, heat or pain ; it is completely insensitive.

The reddening of skin thus anæsthetised is presumably due in part to loss of tone in the vessels, consequent on the withdrawal of the vasoconstrictor nerve impulses, with which the vessels are normally supplied ; it is due, probably in greater part, to an irritant action of the anæsthetic. The skin temperature rises, it may be by 1° or 2°C, and the skin remains red in the congestion test, showing that its arterioles are dilated. The redness of the skin naturally interferes in large measure, though not wholly, with tests of local skin reactions. If the anæsthetic is driven a little deeper into the skin, the colouration is often less intense and more evanescent, though equal anæsthesia is obtained.

Local anæsthesia for several reasons is not entirely satisfactory. Firstly, it produces of itself a more or less pronounced skin reaction, secondly, it discolours the skin and thus confuses observation ; and, thirdly, the precise effect that the anæsthetic exerts upon the nerves is not known except by inference after comparison with other observations. In deeper injections the nerve twigs may be the point of anæsthetisation, in superficial injections the anæsthesia may grip the nerves to their terminal ramifications. The level is thus a matter of some uncertainty ; the method is wanting in exactitude, and its sole recommendations are that it may be applied at any time and to any area of skin.

Cases of nerve degeneration. Patients are selected in whom sensory nerves of the arm have been broken through, cases of old standing bullet injury, and the like, in which the nerves have been caught up and held in dense scar tissue. The corresponding areas of insensitive skin have been tested by Müller (*196*), Ebbecke (*75*), Grant and myself (*164*), Török and Rajka (*249*) ; though it has not always been clear that the nerves have had time to degenerate, this may usually be assumed. Recently my colleagues and I (*167*) have employed instances of recent nerve degeneration following (21 to 50 days) upon surgical section of cutaneous nerves.

Freshly interrupted and degenerating nerves. The ulnar or median nerve may be interrupted, as may smaller cutaneous nerves, by local injection of anæsthetics. In the last case a device employed by Trotter and Davies (*252*)

is useful. If the forearm is searched with a faradic current issuing from a pointed metal electrode, the course of subcutaneous sensory nerves can be traced readily and accurately. When the current passes into skin only, it yields a purely local sensation of pricking ; when it passes into an underlying nerve trunk it causes a throbbing pain that radiates along the nerve's peripheral course. The course of the nerve is followed on the skin, traced back and marked to the point where it emerges from the deep fascia. Normal saline containing 2 per cent. novocaine and 1 in 100,000 adrenalin is now injected at this point. So accurate is this method that the nerve can often be touched with the point of the injecting needle, and the injection of a few c.cms of solution soon causes complete loss of sensation in a large patch of skin ; this state lasts for several hours. The breaking of the nerve path is followed by a slight flush of the skin rendered anæsthetic, but this is evanescent and soon the numbed skin is unrecognisable by its colour.

Skin to which the nerves have been cut surgically has also been investigated a day or two after the section, and the same skin has been tested at frequent intervals for many days subsequently, so as to cover the period during which the nerves are degenerating (*167*).

It will become apparent that abundant tests have been carried out by ourselves and others, when it is known that all these methods of observation have given wholly consistent results.

It is found that when a sensory nerve trunk is *freshly* interrupted surgically or by anæsthesia, the reactions in the corresponding skin are complete in all their details (*164, 167*). The anæsthetic skin yields to a needle scratch a fine red line, to a stroke a red band, to a hot test tube a dull red spot, to a histamine puncture a little circular red spot. Each of these local responses is surrounded by a flare of arterial colour, the full reaction being equally displayed by symmetrical areas (sensitive and insensitive, respectively) stimulated simultaneously. When necessary the local vascular reaction has been given added prominence by the occlusion test, and the flare by the congestion test. The reactions so obtained are quite similar in the sensitive and insensitive skin in these circumstances also. Thus, it is shown that when the reflex arc to the spinal cord is interrupted, by a breach in at least its afferent limb, the vascular reactions of the skin to a variety of stimuli remain quite unchanged.

On the other hand, the reactions of skin to which the nerves have degenerated recently or long ago, or of skin locally anæsthetised, are different. The pinprick, the scratch, the stroke, the burn, the freeze, and the histamine puncture each produces its own local reddening ; none of these nor the galvanic and faradic stimulus (*79*) produces a surrounding flare, though this flare appears, when simultaneous and like stimuli are applied to symmetrical areas of æsthetic skin used as controls.

The flare is lost about the 6th day (*167*), very exceptionally, it may be a week or more later (*164*).

Thus it is shown that the local red reaction is wholly independent of nervous mechanisms ; the flare on the other hand is of nerve origin and depends, not upon the spinal reflex arc, but upon a purely local nervous mechanism. These conclusions are reached for the reaction produced not only by the substance mustard oil, as found by Bruce and Breslauer, but by widely different forms of stimulation, mechanical, electrical, thermal, and chemical. A sufficiently representative series of stimuli has been tested to render it certain that when the response to a stimulus is twofold, comprising a local and dull reddening on the one hand, and a surrounding flare, having peculiarities of its own, on the other, the second is produced by a local nervous mechanism, the first more directly.

The precise nervous elements concerned in the local reflex are discussed more fully in Chapter XV. The channels, as we shall see, prove to be purely sensory.

This inquiry into the influence of the nerves upon the triple response again strongly emphasises the identity of this reaction, produced though it is by many apparently distinct causes. Thus, so far as vascular dilatation is concerned, it may now be said that very numerous and widely different forms of stimulation, when applied to the skin, yield in common :—

(a) A local and active dilatation of the minute vessels, occurring in skin that has neither nerves nor nerve endings.

(b) An independent and widespread dilatation of the strong arterioles that is brought about through a local nervous reflex.

We come next to the wheal.

Factors influencing and controlling the wheal.

Relation to local reaction. The most obvious relation of the wheal to the vascular reaction is its appearance over the precise area that has originally displayed the local red reaction, namely, the area in which the minute skin vessels dilate actively. The stroke wheal, when first it appears, marks out accurately the band of skin redness that precedes it ; the histamine wheal marks out accurately the red spot ; so also with heat and with freezing. From this we may conclude that fluid exudes only from those vessels that participate in the local reaction, namely, those that respond most directly to the stimulus.

Relation to the flare. Oedema produced by stroking the skin of the back occurs, so far as my personal experience goes, and this must now extend to at least 50 cases of urticaria factitia, only in subjects in whom the local red line becomes surrounded by the flare. It is also true in general that if this flare develops, some degree of whealing may be predicted, almost confidently, before it actually appears, and that the brighter and more extensive the flare the more certain it is that whealing will happen. The association between the two phenomena is so close that it has called forth repeated comment and it cannot be regarded as purely accidental.

There are, however, occasional exceptions to the general rule. **Thus,** Ebbecke (*75*) and Parrisius (*203*) both cite cases of whealing to strokes in which they were unable to detect preliminary reddening or substantial reddening of the skin ; apparently, in these cases neither flare nor red line was plain. The only exceptions I have seen have been isolated cases showing flare and wheal on the trunk and, on the arms, a diminutive wheal preceded by a red line only, or by a red line and a barely perceptible flare. In one of the former cases, a surrounding flare could be detected by previously rendering the skin cyanotic. It is to be remembered that some reflex vasodilatation may occur without manifesting itself as a flare in uncongested skin. Similarly the absence of a wheal may not be taken as meaning that there is no œdema.

The relation between a preliminary flare and œdema is emphatic in instances of spontaneous urticaria, the so-called " nettle rash " ; as is well known, the wheal appears centrally in an irregularly circular patch of bright erythema, which precedes it.

If we compare the development of wheal and flare in response to different forms of stimulus, the rule holds good that they are proportioned to each other, though here again there are exceptions. The most notable are perhaps the responses to a faradic current and to mustard oil laid on the skin ; in both these instances the flare is widespread, but whealing may be absent or is inconspicuous by comparison.

Although, in the reactions as a whole, there is an unmistakable relation between intensity of flare and prominence of wheal, it is also quite clear that the flare is unessential to whealing. The most striking evidence for the last statement is that the flare always fails, while the wheal appears to suitable stimulation, when the nerves to the skin have degenerated ; this has been shown for wheals due to histamine, stroking, burning, freezing and faradic and galvanic stimulation (*75, 79, 164, 167*). The wheal is generally of the same size as that produced in control observations upon sensitive skin. The wheals on skin rendered insensitive by local anæsthesia, by which the skin is much reddened, are of reduced size (*164*). Wheal and flare,* or flare and wheal, cannot be brought into the relation of cause and effect.

The meaning of their usual association is different. It is legitimate to say that, when normal skin is stimulated, in all probability the three parts of the complete reaction are always present, unless stimulation has been very weak. A relatively weak stimulus may call forth local vasodilatation alone, or this may alone be visible. As the stimulus strength is increased, reflex vasodilatation and œdema are added or are visibly added in the form of flare and wheal. Experience shows that the intensity of the local red line is a less perfect gauge of strength of stimulation, the phrase including the actual strength of stimulus and skin susceptibility, than is the extent and brightness of the flare or prominence of the wheal. Thus, as strength of stimulation is increased, the conspicuousness of these two independent phenomena will in general be found to increase hand in hand.

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* Other than the secondary flare described on page 54.

Relation to blood flow. A fully developed urticarial wheal projects sharply two or even more millimetres above the general skin level ; the fluid here transuding may be taken for purposes of argument to double the thickness of the skin. This great increase of skin thickness can occur within the space of 3 minutes. We may take the normal supply of blood to the whole arm, when warm and resting, to be between 5 and 10 cc. per 100 cc. of tissue per minute (Hewlett and Zwaluwenburg *116*, Stewart *234*). If we allow that the flow to the skin is in the same proportion as to the arm as a whole, it would take some 10 or 20 minutes to double the skin volume, assuming that the whole blood, corpuscles and plasma, reaching the skin, passed directly from vessels to tissue spaces. If we assume, as we must, that the fluid of the wheal is derived exclusively from blood plasma,* and if we allow further that only half the fluid entering the vessels transudes through their walls, then the flow required to produce a full wheal in 3 minutes would be 7 to 14 times the normal resting flow. The calculation cannot be made exactly, but the argument suffices to make it obvious that an arteriolar dilatation, and a considerable arteriolar dilatation, though possibly unessential to whealing, is essential to *quick* whealing (*159*).

That arteriolar dilatation occurs has been shown, that it is considerable is indicated by the rise of temperature along the line of wheal. This rise may amount in an arm already warm (32·5°) to as much as 2·5°C. That rapid blood flow through the part is an important factor † is also shown, and more directly, by studying the formation of wheals on skin to which the blood flow is deliberately reduced.

The effect of congesting the veins. An armlet is placed on the upper arm of a patient susceptible to stroke wheals and is pumped to the desired pressure. The veins below become correspondingly engorged, the pressure being maintained for several minutes. The arm and the control arm are now stroked, or histamine is punctured into both, and the rate at which wheals develop is watched. A large number of such observations has established the fact that an increase of venous pressure neither expedites the wheal's appearance, nor exaggerates its prominence ; on the contrary, the wheal when fully developed is smaller on the congested arm (*159, 211, 249*). The difference between the two wheals is slight when congesting pressures of 30 to 50 mm. of Hg are used ; it is manifest when the pressures approach or surpass the diastolic pressure in the subject.

That the difference is not due to masking by light general œdema of the congested limb is proved by at once repeating the observation on the two arms, with the congesting pressure now on the arm previously used as a control. The more prominent wheal again appears on the uncongested limb and the difference in the sizes of the two original wheals is maintained. If it

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* Wheals never form on skin in which the circulation is at a standstill.

† Török and Rajka came simultaneously to a very similar conclusion (*249*).

were a question of masking by general œdema * that would not be the case, for œdema of the arm last congested should tend equally to conceal the true size of both wheals formed upon it. When the observation ends, there is a small and a large wheal on each arm ; the small wheal in each case is that formed on congested skin, the large wheal that formed on uncongested skin. Congestion of an arm, on which a wheal already stands, is without apparent influence upon this wheal. These observations of ours possess twofold significance.

Firstly, they may be interpreted, and are rightly interpreted, to mean that diminished blood flow tends to prevent wheal formation (*159*). The wheals are diminished when such venous pressures are employed as are calculated by Stewart (*236*) to produce a notable diminution of blood flow. The higher the venous pressure used, the smaller the wheals ; when pressures approach closely or go beyond systolic arterial pressure, wheals are never formed.

The observations are of interest from a second point of view. The rise in venous pressure must raise to an approximately equal extent the pressure in the minute vessels of the skin ; these vessels become greatly distended and engorged, as witnessed by the deep coloration of the skin during the observation, and by the not infrequent appearance of minute hæmorrhages into the skin when high pressures have been employed. Despite this stretching of the minute vessels, almost or quite to bursting point, despite the greatly exaggerated difference between the pressure within and without these vessels, transudation of fluid to form an urticarial wheal is much diminished.

The walls of the skin vessels may be stretched also, and in like degree, by suction applied to the skin. Ebbecke (*75*) believed such suction to be itself efficacious in producing wheals, but, as I have pointed out (*159*), the evidence upon which he based this conclusion is fallacious. Simple suction, however intense, never produces wheals, even on susceptible skins (see Fig. 28, page 77) ; moreover, applied over a developing wheal, suction, like increased venous pressure, prevents this wheal from forming fully (Fig. 26, page 77).

The foregoing observations show that fluid does not pass from blood vessel to surrounding tissue space to form a wheal as a simple consequence of capillary distension, a distension such as might in that case be supposed to increase the permeability of the vessel walls. Distension is not the cause of increased permeability. Florey (*86*), upon independent evidence, has more recently come to a similar conclusion.

They further contradict the assumption that the fluids pass out into the tissue spaces owing to an increased differential pressure, between the inside of vessel and the tissue space, such as might be thought to quicken filtration.

Moreover it cannot be said that the conditions necessary for whealing are satisfied when such increased permeability, as may be supposed to result from simple distension of the vessels, is combined with a large rise of differential pressure. Obviously a further factor is needed. Can it be said that this consists purely of a normal or increased blood flow ? In other words,

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* As a matter of fact the amount of œdema formed in so short a time is negligible.

is the increased differential pressure, acting upon a wall the permeability of which is supposedly increased by stretching, sufficient to force fluid through that wall quickly enough to form a wheal, granted that this fluid is supplied in adequate amount ? A reply to this question is found, I believe, in the next observations ; and the possible influence exerted by distension and vascular pressure is reduced to narrower limits.

Minimal pressure required to prevent a wheal developing. A heavy stroke is run from the point of the shoulder well down the upper arm on a susceptible skin. The pneumatic armlet is at once applied over the lower half of this line of stroke and the pressure in the armlet suitably raised. The armlet must be in place and exerting pressure before the skin reaction begins. A chosen pressure is maintained for usually 3 or 4 minutes, by which time a wheal has developed fully over the upper half of the line, above the edge of the armlet. The armlet is now removed as speedily as possible and the skin examined. Using this method, it can be shown that wheals will develop against armlet pressure ranging from 30 mm. up to as much as 50 mm. Hg. Higher pressures prevent whealing (*159*). It should here be stated that, once the external pressure is removed, full whealing happens quickly, more quickly indeed than is ordinarily the case, an observation that shows the original stimulus to have been adequate.

The same type of observation may be carried out by stroking the skin, and at once applying over it the mouth of a glass covered capsule ; this capsule is connected previously to a reservoir from which a known pressure may be thrown onto the skin. Subsequent events are watched through the glass window. This method confirms the last in showing that wheals will develop against pressure as high as 50 mm. Hg (Fig. 27, page 77). It shows further that, when the pressure is somewhat higher and just sufficient to prevent a wheal from forming, the flare around the line of stroke also fails to appear in most instances or may appear only faintly, and that a visible red line is either developed faintly, or may on occasion fail to become visible. In other words, a pressure just sufficient to prevent a wheal developing is also just sufficient to suppress the preceding vascular dilatation or, more usually, sufficient conspicuously to reduce it (*159*).

Thus it is shown that the increased pressure developed in the vessels in response to the stroke is counteracted in some instances completely or almost completely by the external pressure applied. A slightly lower pressure permits fluid to pass out of the vessels ; here distension of the vessels is small and the differential (vessel to tissue) pressure cannot greatly exceed the differential pressure in normal surrounding skin. It is to be remarked that the pressure needed to prevent the appearance of the red line, and the pressure needed to abolish it once it has developed, do not differ materially in those prone and in those not prone to wheal, provided that the control subject is one in whom reddening to stroke is vivid. The evidence presented in these pressure determinations shows that filtration under an enhanced pressure may be disregarded in discussing the cause of wheal œdema ; it certainly

Fig. 26.   (× ½).   *Effect of suction upon a developing wheal*.   The back of an
          urticarial subject was stroked and a suction capsule at once applied
          at -70 mm. Hg over the centre of the line.   At the end of 3 minutes
          the capsule was removed and the photograph taken.   Outside the
          limits of the capsule the wheal has fully developed ; within, it is much
          reduced in size.

Fig. 27.   (× ½).   *Effect of a critical pressure upon a developing wheal*.   The
          arm of an urticarial subject was stroked and a pressure capsule at
          once applied at 40 mm. Hg.   The capsule was removed at the end of
          4 minutes, and the photograph immediately taken.   It shows a full
          wheal above and below the compressed region, and a slight but
          perfectly distinct wheal over the part of the stroke line that was
          included within the capsule.

Fig. 28.   (× ½).   *Suction fails to produce whealing*.   The back of an urticarial
          subject was firmly stroked and at the same time a suction capsule
          was applied to the skin at a pressure of -90 mm. Hg.   At the end of
          4 minutes the capsule was removed and the photograph taken.   The
          stroke has produced a full wheal ; the margin of the capsule has
          depressed the skin ; there is no whealing of the skin exposed to
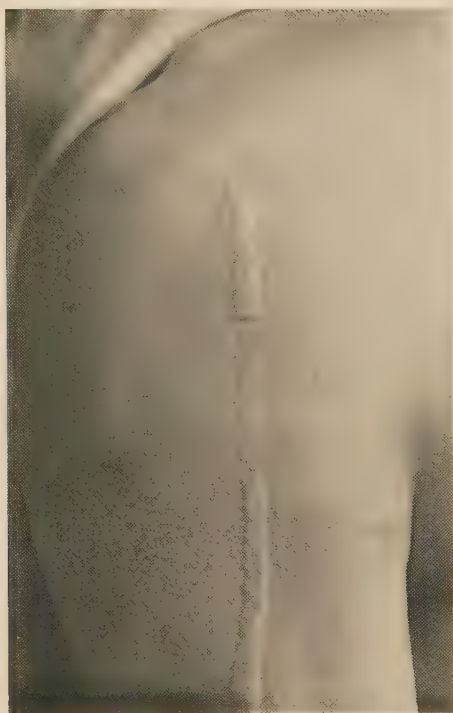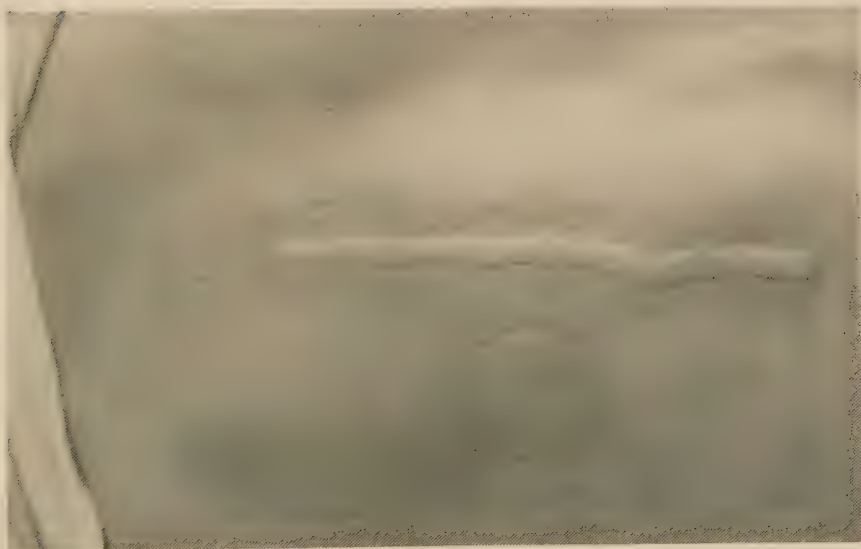   suction.

Fig. 26.

Fig. 27

Fig. 28.

places simple filtration hypotheses finally out of court. For if pressures gauged to be as great as 70 mm. Hg or more, the pressure frequently required to prevent the appearance of the red line in the control subject, are developed in the minute vessels of the skin without œdema following, pressures exceeding these by at least 40 or 50 mm. Hg would be required to produce whealing of a susceptible skin under our capsule. The full calculated pressure required would then approach or would sometimes actually surpass, the systolic pressure in the arteries of the subject tested.

The same observations and the conclusions drawn from them, while disposing of the view that a sufficient increase of permeability can result from simple stretching of the vessel walls, at the same time convinces us that a conspicuous increase of permeability actually occurs. It is true that wheals, developing under a counteracting pressure, are diminutive : but this is due simply to the check imposed upon blood flow through the tissues pressed upon ; it is even possible in these circumstances that increased permeability may be the sole factor determining œdema. Under more natural conditions, however, increased permeability will not suffice ; it must be associated with greatly increased blood flow.*

The experiments here described apply to wheals formed in response to the stroke stimulus. Others, covering substantially the same ground, have been undertaken with wheals developing in response to a histamine stimulus (*164*). The results are in close agreement and the present conclusions apply to wheals produced in both ways.

A further evidence of increased permeability is to be found in the protein content of the fluid formed in the stroke wheal. This may be gauged approximately in the following way. If several capillary glass tubes are thrust into a fully developed wheal, and gentle pressure is then exerted on the wheal, it is possible to collect a cubic millimetre of clear fluid. Such a quantity is drawn up and diluted ten times in graduated capillary tubes and mixed with an equal part of absolute alcohol. At the same time an equal quantity of the subject's blood serum diluted 10, 12, 15, 18 or 20 times is drawn up into separate tubes, and an equal part of alcohol added to each. The tubes are sealed and the precipitated proteins are then compared, before and after centrifugalisation. The wheal fluid 10 times diluted is judged to contain an equal amount of protein to that found in the serum diluted 12 to 15 times (*159*, see also Török *246*). Thus the protein content of wheal fluid approaches very closely that of blood serum itself, much more closely than does the protein content of lymph collected from the limb (see Starling *232*) or the fluid drained from dropsical patients. The wheal fluid forms perfectly distinct clots of fibrin, in which a few leucocytes are enmeshed, soon after it is withdrawn ; this clot is removed, as is that of the subject's blood plasma, before the protein is estimated.

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* If a stroke is made on the skin of a normal subject and this is just sufficiently heavy to produce perceptible œdema, then by puncturing in histamine near the line of stroke a minute later, thus increasing the blood flow to the line of stroke, more conspicuous whealing along the line of stroke usually results. Sometimes this effect is remarkable.

A final observation confirms the general argument that vascular dilatation due to enhanced differential pressure and accompanied by an appropriately increased blood flow, does not suffice to produce wheals, and again points to a primary increase of permeability as the chief cause. If suction is applied to the region of flare surrounding the local red line of a developing wheal, a dilatation of the vessels controllable in its degree is added. However great this dilatation, the suction fails to raise a wheal, although all the recognised and simple vascular conditions appear to be fulfilled. What is lacking is the stimulus of the stroke, the change in permeability of the endothelial wall that this stroke provokes being requisite for the rapid outpouring of fluid.

To sum up, œdema, like the local vasodilatation and like the surrounding flare, is part and parcel of the total reaction that follows a large number of widely differing forms of stimulation. The wheal, like the flare, is less in evidence when stimulation of the skin is relatively mild ; both are manifest when stimulation is relatively strong. The outpouring of fluid into the tissue spaces is not the result of an increased filtration pressure. The increased permeability is not the result of simple stretching of the vessel's wall ; it is the result of an independent change in the wall in response to stimulation, whereby this wall becomes unusually pervious. Once this increased permeability is established, the rate at which fluid is poured out is mainly governed by the rate at which blood is supplied to the very pervious membrane.

It is expedient to state that these conclusions are applied for the moment only to the form of œdema discussed ; they may be and very probably are relevant to more gradually forming œdema, though this question properly remains for future observations to decide. It is also to be said that further evidence, if such is needed, that the increased permeability of the endothelial wall is independent of the size of, and pressure changes in, the minute vessels involved in the vascular reaction will be found in experiments described on page 96.

Duration of the period of transudation. The wheal comes to its full height in from 3 to 5 minutes. This fact suggests that it is only during this period that fluid actually leaves the vessels ; it does not prove the point, for it is conceivable that at later stages transudation and reabsorption by blood vessels and lymphatics effect a balance. An ingenious experiment by Ebbecke (*78*) shows that this is not the case. If trypan red (or blue) is injected into the general blood stream, the dye appears in the wheal while it is forming, but does not discolour a wheal already developed. He thus shows that transudation ceases in about 5 minutes, and at the same time demonstrates that absorption of the fluid must be extremely slow, since the uncoloured wheal may last for several hours. Incidentally Ebbecke's observation further demonstrates increased permeability of the vessel walls, since the natural vessel retains these dyes. The reason why transudation ceases in so short a time will be discussed in a later chapter.

CHAPTER VI.

A RELEASED SUBSTANCE THE CAUSE OF THE TRIPLE RESPONSE.

FROM the evidence of the last two chapters we arrive at the conclusion that numerous and widely different forms of stimulation yield in common three distinct events. These are :—

(a) a primary and local dilatation of the minute vessels of the skin.

(b) a widespread dilatation of the neighbouring strong arterioles brought about entirely through a local nervous reflex, and

(c) locally, increased permeability of the vessel walls.

The object of this reiteration is to impress two facts. Firstly, that the complete reaction is not single but complex ; it comprises in reality three mutually independent effects. Secondly, that this complex mechanism, involving as it does two actions on the vessel wall and one action on the nerves, seemingly can be provoked by stimuli of very different kinds, namely, mechanical, thermal, electrical and chemical. If a number of apparently distinct causes were known to lead to one simple end result, for example, reddening of the skin, we might be led to suppose such reddening to be brought about in several distinct ways ; but when the end result is as complex as it has been shown to be, and when the complete reaction, however produced, has the measure of constancy here displayed, an explanation along these lines is not open to us. We are forced to search for a common causative factor, interposed between the apparent stimulus and this reaction. A very little reflection suggests this common factor to be connected intimately with tissue injury ; for each form of stimulus employed, acting in somewhat greater intensity, kills the cells of the skin *en masse*.

Another method of reasoning brings us towards a similar conception.

Susceptibility of urticarial patients to histamine and other noxious substances.

It is obvious that in urticaria factitia the skin is hypersensitive to stroking, responding by the production of prominent wheals. This susceptibility might be peculiar to the mechanical stimulus or it might be a more general susceptibility. The first is found to be the case. The pin prick and scratch being mechanical yield exaggerated reactions ; the faradic and galvanic

current, burning heat and freezing have no greater effect in urticarial subjects than in controls.*   If histamine is punctured into the skin of these subjects, or if in its place, morphia, atropine sulphate, or lactic acid is used, the resultant wheals are no larger than in controls similarly tested (*164*).   If we inquire from our patients as to the effect of gnat bites or nettle stings upon them, we arrive at the same result ; they react normally, though with variations similar to those experienced by control subjects.   The susceptibility to the mechanical stimulus is one which stands by itself.

Now, if the proneness of urticarial subjects to flare and to wheal consists of an unusual reactivity of the vessels, then the stroke and the histamine stimulus, producing similar vascular reactions as they do, would both be expected to yield exaggerated reactions ; in actual experience they do not ; response to the stroke is alone conspicuous.   Having concluded that the same complex mechanism is set in motion by distinct forms of original stimulus, and having seen that it is here set in exaggerated motion by the stroke only, then it becomes incredible that the exaggerated reaction is due to increased susceptibility of the mechanism stimulated.

We arrive at the conclusion that, for some reason, a single stroke forms in an urticarial subject an adequate stimulus to a mechanism composed of such nervous and vascular elements as are involved and that is no more than normally excitable.   Now, since the stroke is a similar stroke to that put down on the skin of the control subject, and which, if unrepeated, yields but a limited response, we are led to doubt if this stroke itself provides the impetus that sets the train of events in motion.

Again, we have seen that a light stroke produces a white reaction, resulting from contraction of the minute skin vessels ; a firm stroke produces a red line, due to dilatation of the same vessels. Apparently the first forms a stimulus to contraction ; does the second indicate a direct response in the form of relaxation, as has hitherto been supposed ?   The natural reaction of involuntary muscle to mechanical stimuli is contraction ; relaxation in direct response to a stronger stimulus of the same kind has not been described to my knowledge.   To explain the red line as a direct response cannot be regarded as satisfactory therefore.

These considerations bring us back to the question of tissue injury and force us to ask if the susceptibility of the skin of the urticarial case is not really a susceptibility of its cell elements to mechanical injuries ; for example, an unusual fragility, or may be a departure from the usual grade of metabolic stability upon the receipt of these forms of minor damage ?   The question is in part answered, and our enquiry is carried a stage farther by the following observations.

* A statement based upon unpublished observations.

Diffusible substances responsible for local vasodilatation in normal and
urticarial skins.

It is notable that the red line, produced by a stimulus that is just
adequate on an arm in which the circulation has been stopped, does not
subside ; it persists at maximal intensity so long as circulatory arrest is
continued (tested up to 25 minutes). If a corresponding stroke is put down
on the normal skin, the red line fades and often becomes imperceptible in
the same period. This observation, made independently by Ebbecke * (*79*)
and ourselves (*164*), suggested that the stimulus directly producing the local
red line persists in its full force throughout the period of arrest, and again
pointed to the deduction that the stroke does not form the direct stimulus.
While suggestive, there is nevertheless an element of uncertainty in this
evidence, since, after fading, the red line may reappear on the normal skin
at a later period, and the meaning of this reappearance is not as yet fully
understood. The question is brought to a more decisive issue by the following
tests.

Spread of local skin reaction. If histamine (1 in 3,000) is punctured into
normal skin, and the site of puncture is watched for the first sign of whealing,
this may be seen in about 1½ minutes. The diameter of the wheal at its
appearance is approximately 2 millimetres, but, while it is growing in height
during the next few minutes, its diameter may more than double. A similar
though proportionately smaller spread is seen in instances of stroke wheals.
Now this resemblance between the histamine and stroke wheal is not neces-
sarily significant, because it may be argued that the fluid, gathering under
pressure in the skin, naturally tends to shift into adjoining tissue spaces.

Of more significance from this standpoint is the following experiment.
The normal forearm is congested by throwing a pressure of 30 mm. Hg upon
the veins, and after a few minutes the pressure is raised to 200 mm. to arrest
the circulation to the limb. Histamine is now punctured into several parts

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* The main line of reasoning that led this worker (*76, 77, 79*) to regard substances liberated
in the skin as responsible for the vascular reaction that follows, a hypothesis at which Grant and I
were arriving independently, has been shown to be unsound. Briefly it was as follows. The
high resistance of the skin to constant currents is generally believed to be due to polarisation of
the skin. Ebbecke found that this resistance is greatly reduced by rubbing the skin or by passing
through it a galvanic current of sufficient strength to produce whealing. He therefore regarded
the lowered resistance as an indication that the living cells of the epidermis become excited to
activity, for a similar change occurs in nerves and muscle when they are stimulated; their original
polarity is lost and their resistance falls. The released metabolites were regarded as influencing
the blood vessels. This hypothesis was based upon his showing, as he thought, that the lowering
of resistance occurs in the living cells of the epidermis. Zotterman and I have shown that his
evidence for this conclusion is untenable (*176*), and that the lowering of resistance is due to breaks
produced mechanically in the horny layer of the skin, either as a result of friction or by the
disruptive influence of hydrogen bubbles (see page 58). We have shown that the great resistance
to constant currents is not appreciably lowered, when the skin reacts vigorously to burning heat
or freezing, and that there is in fact no relation between the response of the skin and lowering
of its resistance to galvanic currents ; but that the resistance is lost if a needle point is driven
into the horny layer of living or dead skin. Ebbecke's observations upon skin resistance can no
longer justifiably be regarded as supporting the view that released metabolites are responsible
for the vascular reactions ; consequently I have not thought it desirable to discuss his experiments
more than briefly here.

of the skin, the skin is lightly vaselined to protect it, and the arm is laid in a bath of water at about 18 to 20°C.* Shortly, small purple spots appear at the sites of puncture. They rapidly become more sharply defined and proceed to *increase in diameter*. The spots remain clearly defined and no wheals form on them until the circulation is restored. Wheals then quickly appear and their diameters, when they are at first sufficiently defined to measure, correspond accurately to the full diameters of the purple spots that they replace. Thus, although the circulation is brought to a standstill, the area of minute vessels dilated and rendered permeable locally by histamine notably increases, doubling itself in about 8 minutes.

The reason why this increase occurs in the vascular territory affected is hardly in doubt. Histamine has been forced into the skin along a fine needle track and, when the circulation is at a standstill it diffuses slowly in every direction and, to judge from the circular shape of the spots, almost uniformly through the surrounding skin. Some such spread no doubt occurs in skin to which the circulation is free, for wheals developing in these circumstances cover an area greater than that damaged by the needle ; but, as has been pointed out, this spread may be attributed, partly at all events, to shifting of the fluid gathering under pressure. When gradual and regular spread of the local vascular reaction occurs on an arm to which the circulation has been arrested, simple diffusion of the poison will alone explain it.

Now, if similar observations are carried out on urticarial subjects, the histamine puncture being replaced by a stroke, a similar encroachment of the purple line upon the surrounding skin is witnessed, even while the circulation is stopped and the arm cooled. Moreover, the wheals that subsequently appear on releasing the circulation are broader, *when they first become defined*, than are those that form on a normal arm (*164*). The spread of the purple line, and the spread of the area of increased permeability, thus displayed and advancing hand in hand with it, are to be interpreted as in the parallel observation with histamine. The comparison is important because in the latter case we know that a diffusible substance has been introduced, and we expect diffusion to occur during the period of circulatory arrest. Seeing a similar event happen in the case of the purple line, we are led to conclude that the stroke has liberated within the skin a diffusible substance, which acts like histamine as a direct stimulus, dilating and increasing the permeability of the vessel with which it comes in contact.

This conclusion is also compatible with other observations. If we choose the arm of an insusceptible subject and stroke it in similar circumstances, the purple line soon appears ; but while the limb vessels remain closed the diameter of the line does not increase measurably, and no wheal appears at the release. If we assume, as we must under our hypothesis, that the stroke here liberates the diffusible substance, the absence of visible spread is to be

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* This cold bath is necessary, since, as we shall see, it preserves such increased permeability of the vessels as is produced by the histamine.

explained by its liberation in insufficient quantity. Locally the substance is liberated in a concentration adequate to dilate the vessels, but not to increase their permeability in notable degree. Spread of the reaction requires not only diffusion but a diffusion sufficient in amount to bring the concentration to a definite level in the surrounding skin. If, instead of stroking the normal skin once, the stroke is repeated several or many times, the vascular reaction is now seen to spread and, upon releasing the circulation, whealing promptly occurs. The last example is similar in every respect to the reaction of an urticarial subject, except for the necessary repetition of the stimulus.

It is concluded that, when the skin is insusceptible, a single stroke liberates a diffusible substance in relatively small amount, that its concentration is sufficient manifestly to produce only a strictly local vasodilatation, and that diffusion in adequate concentration to surrounding skin does not happen. But if the stroke is repeated, or if a single stroke is put down on a susceptible skin, the quantity released is greater, its concentration is higher and, as the substance diffuses, an adequate concentration is also reached in the immediately surrounding skin ; this now manifests both vasodilatation and whealing (*164*).

It may here be added that a similar spread of the local vasodilatation to that described in the case of histamine and stroking occurs when normal skin is burnt, frozen or stimulated by means of galvanic or faradic currents (unpublished observations with Grant and Marvin).

We next proceed to examine the flare along similar lines.

The flare is due to a chemical stimulus.

When histamine is punctured into the skin, a surrounding flare appears in about 20 seconds, spreads, reaches its height in about 3 or 4 minutes, and subsequently fades. The flare produced in response to histamine, punctured into an urticarial skin, is not perceptibly brighter nor more extensive than is that produced on insusceptible skin. As in the case of the local wheal to histamine, so in the case of the reflex histamine flare, skin insusceptible and susceptible to stroking both yield similar reactions. It is not that the nervous mechanism is unusually excitable ; it is that the stroke applied to the susceptible skin releases a stronger stimulus. When histamine is punctured into the skin, the surrounding flare might be attributed to the immediate effect of the prick, for that also produces by itself a surrounding flare in both normal and urticarial skins ; it might be attributed to the histamine introduced ; or to the combination. It is easy to show that the first forms an inadequate explanation, since histamine flares are very notably brighter and more extensive than prick flares. Moreover, the appearance of a flare around the site of a prick on a normal skin is insufficient evidence that the prick constitutes the stimulus ; alternatively we may suppose that the prick, by damaging the tissues, itself liberates a small quantity of

chemical substance ; that is a question to which we may profitably return presently.

Apart from its more vivid colour and extension, evidence is forth-coming, both in the case of normal and urticarial skins, that the greater part of the flare surrounding a histamine puncture is due to the action of this substance. The evidence consists in showing that the fading of the flare can be deferred by arresting the blood flow to the skin observed. If a
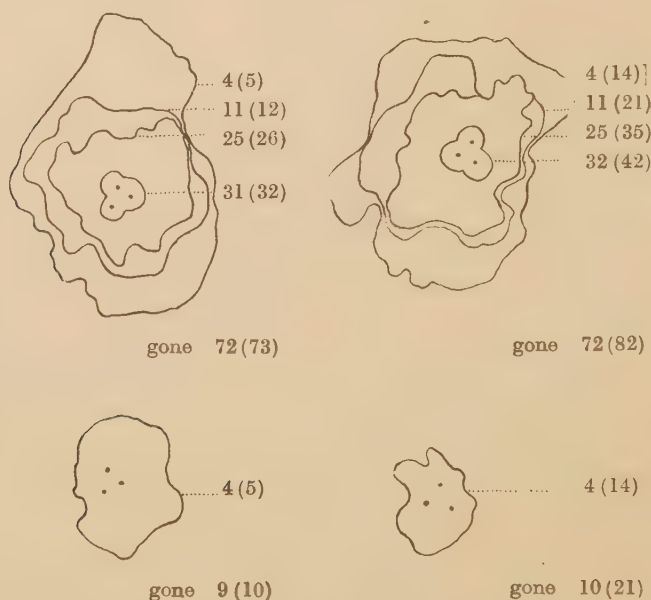

4 (5)
11 (12)
25 (26)
31 (32)

4 (14)
11 (21)
25 (35)
32 (42)

gone 72 (73)

gone 72 (82)

4 (5)

4 (14)

gone 9 (10)

gone 10 (21)

Fig. 29 (× 2/3). Normal subject. In this and the succeeding figure, the left outline corresponds to a left arm area and the right to a symmetrical right arm area of skin. The vessels of both arms were occluded ; a group of three histamine punctures (1 in 3,000) (above), and a group of three simple needle pricks (below) were put down on the right forearm ½ minute after the occlusion and on the left forearm 10 minutes after the occlusion. The circulatory arrest was continued in each to the 11th minute, when both arms were released. The outlines of the flares aroused by the stimuli were outlined at fixed times after the release of the vessels and these times are expressed in minutes against the corresponding contours. The numbers in brackets represent the corresponding times elapsing after the stimuli were laid down. The times at which the flares disappeared completely are also noted. The positions of the punctures are also shown.

group of closely set histamine punctures (1 in 3,000) is laid down on the skin of the forearm, the flare soon appears, spreads, becomes more vivid, and fades. In most subjects this fading is far advanced 10 minutes after the puncturing. If a similar group is laid down on the forearm, the vessels supplying which have been closed previously, and if the occlusion is main-tained for ten more minutes and then released, the whole arm at once becomes

brightly hyperæmic (see Chapter XI). This general hyperæmia shortly fades away from all parts except the vicinity of the histamine punctures. The histamine flare soon becomes defined and its fading is watched and compared with that surrounding histamine punctures on the control arm. Accurately to compare the events on the two arms, it is necessary that both should experience the general hyperæmia following release of the circulation, for this general hyperæmia modifies in some degree the subsequent events. The experiment is therefore performed as follows :—the arms of the subject are examined, and they must be of equal temperature. The brachial vessels of both arms are compressed pneumatically and they so remain for 11 minutes. At the end of the 1st minute, histamine is punctured into one arm and, at the end of the 10th minute, it is punctured into the second arm. Now the arms have been similarly treated, except that histamine punctures have been laid down on the one 9 minutes before they have been laid down on the other. At the 11th minute, the arms are simultaneously released ; a bright and equal hyperæmia soon covers both ; as this fades the histamine flares become defined, usually about 3 minutes after the release. They are quickly outlined in ink on the skin and, as they fade and shrink, they are outlined one or more times at convenient intervals. We then possess two diagrams such as those shown at the top of Fig. 29 and can compare them. The values set against the contours represent the corresponding times from the release of the circulation (those in brackets represent the times that have elapsed since the skin has been punctured). Corresponding contours (right and left) naturally vary in form and, one way or the other, in extent ; but in general they are remarkably alike. The fading on the two arms occurs simultaneously, it occurs in the same fashion, including the appearance of speckling ; it is impossible at any stage of fading to decide, from the appearance of the two arms, which was punctured first. In other words the period of circulatory arrest, intervening between the puncturing of the two arms, corresponds precisely with the period (measured from the time of puncture) by which the fading of the flare is postponed on the arm first punctured. That is so whether the period in question is 5, 10 or 15 minutes. The natural interpretation of this delay in fading is as follows. Histamine has been pricked into the skin while the circulation to the skin is stopped ; it is retained in the skin and its usual and full action in producing a flare is seen at the release. It is inconceivable that the flare remaining on the arm when the circulation is released is due in any part to the original mechanical or painful stimulus of pricking. A simple reflex vasodilatation so caused would subside in equal, or almost equal, times from the application of the stimulus, whether the circulation to the limb was stopped or not ; it would not be delayed by the time of the occlusion period.

　　The conclusion, which Grant and I reached, that fading is delayed because histamine is retained in the skin, has little intrinsic interest. It becomes important when it is applied. If we find that arresting the circulation for a fixed period of time delays by precisely that period of time a reflex flare,

which might otherwise be attributed directly to a mechanical stimulus, we may place such a mechanical stimulus out of court as the direct cause of the flare, and we obtain strong evidence that the immediate cause is a chemical stimulus, as in the case of the corresponding histamine experiment.

For this reason Grant and I (*164*) repeated the observation, now using urticarial subjects and substituting strokes for histamine punctures. We did so in keen expectancy that we should obtain, one way or the other,
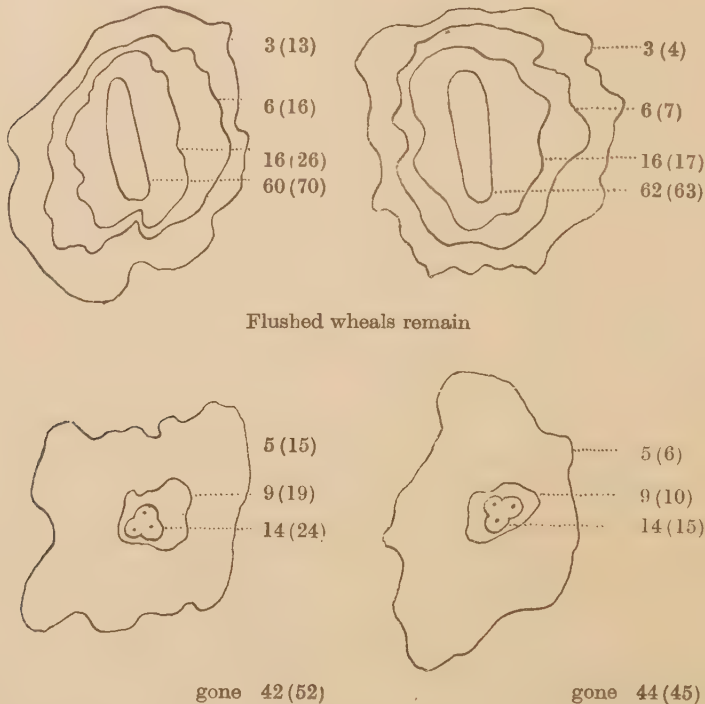

3 (13)   3 (4)

6 (16)   6 (7)

16 (26)   16 (17)
60 (70)   62 (63)

Flushed wheals remain

5 (15)   5 (6)

9 (19)   9 (10)

14 (24)   14 (15)

gone   42 (52)   gone   44 (45)

Fig. 30 (× 2/3). Urticarial subject. The vessels of the two arms were occluded. One minute later the left forearm was stroked (above), and a group of three histamine punctures (1 in 3,000) was laid down (below) ; at the 10th minute, or 9 minutes later, the right forearm was similarly and symmetrically treated, both arms being released at the 11th minute. The contours of the areas of flare are shown as these fade away. In the stroke figures, the fading was followed until the redness became confined to the wheals.

decisive evidence in respect of the central problem of our studies. The flare that develops around such a stroke behaves in precisely the same way as does that surrounding histamine punctures, as we were able to ascertain in repeated tests. The contours of fading on the two arms present the parallelism previously described, and are illustrated in Fig. 30.

A similar statement applies to the flare surrounding a simple needle prick (Fig. 29), that which surrounds the application of burning heat to the

skin (*164*), that which surrounds a frozen area (*171*), or the point at which a galvanic current has been applied (unpublished observation). Each and all of these flares are delayed by the precise period of time that intervenes, during circulatory arrest, between the application of the first stimulus and its control.

It is concluded, therefore, that when a surrounding flare follows a stimulus, whether the stimulus consists of a stroke, prick, freeze, burn or galvanic current, this original stimulus is not itself responsible for the flare ; the original stimulus, so Grant and I concluded, acts by damaging the tissues and by liberating a substance in the skin, which substance then provokes the reflex vascular reaction.

The first conclusion stands unquestioned, the second has become subject to further consideration,* but remains unaltered.

That both are true is shown by further experiment. Histamine (1 in 3000) is punctured into two parts of the skin of the arm, one above the other, and equal flares and equal wheals are allowed to develop. When this has happened, an Esmarch's bandage is tightly wound several times around the arm so that it includes the lower wheal. The bandage is maintained in position, and the circulation to this wheal is stopped for as long as 20 minutes. Half of the corresponding flare is visible above the bandage and the circulation in this skin is intact ; this part of the lower flare retains its original brilliancy and extent throughout the experiment, while the upper or control flare gradually declines in size and its colour fades. This observation shows that if histamine is introduced into the skin and is kept there by preventing blood circulating in its neighbourhood, it continues to act on the nerve endings and is capable of maintaining a flare in distant skin in which the circulation is still free. When this experiment is repeated, using the stimulus of galvanism, burning heat, freezing or the stroke upon susceptible skin, instead of histamine, exactly similar events are witnessed ; such being the case, it is clear that these physical

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* It has been reconsidered in consequence of certain unpublished experiments which Grant, Marvin and myself have made with local anæsthetics. If, within 1, 2 or sometimes 3 minutes of stimulating the skin with histamine, galvanism, burning heat or by freezing (the stimulus being confined to the superficial layers of the skin), a few drops of 1 per cent. novocaine are forced into the skin over an area covering the site of stimulation, the flare from the original stimulus quickly subsides ; it is not maintained as is a control flare. Now this observation is entirely consistent with the conclusion that, in the case of the physical stimuli, we have to deal with a substance liberated locally, and it seems to be compatible with no other conclusion; for any direct stimulation of the nerve endings of the skin by the stimulus applied is long since complete when the nervous impulses are abolished by the anæsthetic. We have found, however, if the anæsthetic is introduced as long as 4 or more minutes after the end of stimulation, that the flare is then maintained as long as it is if no anæsthetic is introduced. This observation suggested the possibility that the flare might be maintained during circulatory arrest not by the chemical substance released locally, but by a substance released distally, namely, in the skin that actually presents the flare. The evidence for this distal release is unconvincing, however ; further observations seem to show that the failure of late anæsthesia to affect the flare is due to the substance released locally moving deeply, and to our consequent inability to reach with the anæsthetic all the receptor nerve endings involved. Our observations in this connection are too recent and numerous fully to consider here ; but we have been able to obtain new and as we think quite conclusive evidence that the flare is originally caused by a substance released locally and this is the matter with which we are now alone concerned. This evidence is that next given in the text.

agencies do not act upon the nerves directly, but that they release a chemical substance locally, which is retained under the bandage and continues to stimulate the receptor nerve endings. It is to be added that we have been unable to prolong the duration of any part of the flare, if the actual site of stimulation is not included beneath the bandage.

To sum up, it has now been shown that the constituent parts of the triple response cannot legitimately be attributed directly to the physical stimulus. There is evidence that a diffusible substance is liberated in the skin and is responsible for the local reaction by its direct effect on the vessel wall ; it is shown that a chemical substance is liberated and yields a widespread arteriolar dilatation by acting on a local nervous mechanism. It would be gratuitous here to postulate more than one substance, since one suffices.

We postulate a substance resembling histamine in its action, since such a substance if liberated would unquestionably produce the triple response precisely resembling that following various physical stimuli.

The close resemblance between the reactions induced by a number of forms of stimulation, viewed generally or in detail, serves to link them all together ; the reactions are plainly similar or identical and behave alike in a variety of circumstances. The evidence, treated as a whole, is sufficient to convince that any reaction conforming in its details to the type reactions described, and reasonably explainable in terms of cellular damage, is of the same fundamental kind. I therefore extend the conclusions to chemical stimuli ; for these are known to produce tissue injury and they are known to provoke the triple response.

The conclusion when it relates to chemical stimuli cannot be tested upon the lines laid down in this chapter ; for if an irritant substance is introduced into the skin, it will itself spread, it will itself be held up by circulatory arrest. The reasons advanced for the inclusion of the irritant substance in the extended conclusion are sufficiently forcible. Some further evidence will be considered when we take up, and compare with the acute reactions here described, forms of stimulation that act more slowly, and this evidence is favourable to the conclusion. It is also to be pointed out that, if we refuse this conclusion, we are left with a single alternative, namely, to conclude that a large variety of substances, including acids and alkalies, the last two known to exert in weak concentration directly opposed influences on the vessels, are capable of reproducing, by a direct influence on the tissue elements concerned, the three constituent parts of the triple response that in the case of physical injuries are attributed to our common chemical substance. They must not only produce these three reactions, they must reproduce them together, in measurable and constant proportion, in measurable and constant time intervals. So stated this alternative conclusion becomes untenable.

From the analytical foundation of this and previous chapters I take the further step, and by induction conclude that whenever the skin displays

the prompt triple response here described and explained, this triple response is due, irrespective of the circumstances in which it appears, to the release in the skin of a common chemical substance.

I would add to this generalisation that the triple response is due entirely to this cause, but must in so doing make one slight reservation. It applies only to two forms of stimulus, of those with which I am familiar, namely, faradic stimulation and oil of mustard. In both these instances the extent and intensity of the flare seems out of proportion to the intensity of the local reaction. While there is little doubt in my mind that the flare produced by faradism is also brought about mainly in the manner described, and that it is not mainly due to direct stimulation of the nerves, yet it does not always behave as do the flares previously described ; for this reason final judgment of the faradic flare is reserved until further observations, now in progress, are complete.

In arriving at the broad conclusion, there have also been in my mind certain phenomena, which are as yet undescribed in this book, and these led me at first to hesitate in putting forth the generalisation. These phenomena are the slower but similar reactions to other forms of stimulus such as ultra-violet light, and the eruption termed herpes zoster. As will be seen in later chapters, these phenomena no longer stand in the way. We shall not at once consider them, but shall proceed in the immediately succeeding chapters to examine further evidence in support of the primary conclusion, that in acute reactions a chemical substance is released, and to consider the nature of this substance.

Chapter VII.

THE EFFECTS OF TEMPERATURE AND CIRCULATORY ARREST UPON WHEALS.

In Chapter V it has been concluded that the increased permeability of the vessel wall is independent of vascular dilatation. In the present chapter more evidence is given for this conclusion and also for the conclusion that injury to the skin is accompanied by the liberation of a substance to which the visible reactions are due.

Effect of cooling the skin.

If before or immediately after stroking the skin of an urticarial subject or puncturing in histamine (1 in 3000)*, the skin is immersed in water at 12° to 15°C, the rate at which wheals develop is much retarded as compared with those developing in skin at normal temperatures. At the end of 5 minutes the wheals are still diminutive, but, if the cold water is withdrawn or the skin is reimmersed in water at 36°C, the wheals come to their full size in about 15 minutes. The reduction in the size of the wheal is greater in the case of histamine than in the case of the stroke ; in other respects the effects of cold are the same in the two instances (*164, see also 126*).

The more gradual development of wheals in cold skin is sufficiently explained by a decrease in the supply of blood to it (*164*).

Effect of heating the skin.

If the forearm of an urticarial subject is immersed† to a marked line in hot water (45° to 47°C) for 3 minutes ; if the skin is stroked vertically and firmly across the line of immersion and the arm is reimmersed to the same line, a wheal develops on the unheated skin only, or develops much more fully on this skin. Similar results, though they are somewhat less conspicuous, are seen when a row of histamine punctures is similarly tested, whether normal or urticarial skin is used (*164*).†† If the stimulus is put down

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* The strength of the base that is always used unless it is stated otherwise.

† It is customary always to coat the arm thinly with vaseline before immersion, to protect the skin from moisture.

†† These observations have been confirmed by Török and Rajka in the case of urticaria factitia, histamine, morphine and atropine wheals (*250*).

first and the arm is subsequently heated, the effect varies according to the ,
time interval that elapses between stimulation and heating. When the
stimulus is laid down from 1 to 1½ minutes before heat is applied, wheals
develop fully or almost fully ; the shorter the interval, the greater is the
reduction (*164, 250*).

The failure of whealing when the stimulus is applied to a hot skin, is
believed to be due to the substance liberated by stroking, or histamine
itself, being washed away more quickly when the blood flow to the skin
is rapid ; full whealing occurs only if the liberated substance or histamine
is allowed sufficient time to grip the tissues before heat is applied. The
evidence for this view is not as simple as might at first be thought, so that
it is convenient to defer its further discussion.

Effects of stopping the blood flow to the skin, and of varying temperature in this circumstance.

An armlet is placed on one upper arm of an urticarial subject, and
sufficient pressure is thrown into it to occlude the vessels. Strokes and
histamine punctures are now laid down on both arms. On the arm to which
the circulation is stopped no wheals develop, and this is so as long as the flow
of blood is stopped ; on the control arm wheals quickly appear. If, however,
the circulation is restored to the first limb as soon as the control wheals have
developed, whealing quickly happens on this skin also. These facts have
been mentioned previously, but certain further and interesting phenomena
require notice. If the circulatory arrest is maintained beyond a certain
period of time, whealing at the release is reduced in amount ; and, if the
arrest is very long, wheals fail to appear at the release (*164, 211*). The actual
time relations vary in different subjects and with different temperatures ;
an occlusion lasting 5 minutes may suffice to prevent subsequent whealing,
or the time required may be much longer.

Effect of heat. If histamine is punctured into the skin of an arm to
which the circulation has been arrested, and this arm is immersed for
from 3 to 8 minutes in water at 43° to 45°C, then at the release no whealing
happens or the wheals are much reduced in size.

To analyse the meaning of this observation more precisely the following
procedure is used. The arm vessels are compressed and remain so ; one
minute later three groups of histamine punctures are laid down on the
forearm in the positions shown in the accompanying diagram (Fig. 31).
The three groups are termed *A*, *B* and *C*, respectively. All groups are now
quickly and thinly coated with vaseline and the arm is placed obliquely
in hot water, so that the skin is covered up to *line 1* of the diagram. The
arm is kept so for a period of from 1½ to 3 minutes, and is then brought
upright so that the water rises to the horizontal *line 2* ; here it is maintained
for another period of from 1½ to 3 minutes. The most suitable times and
temperature are obtained by trial. The arm is withdrawn, lightly wiped

and the circulation in it re-established.   Large wheals develop in group *A*
and, if suitable temperature and times have been used, reduced wheals appear
in group *B*, while in group *C* they are slight or absent.   Now all the groups
have been deprived of circulation for the same time, all experience a transient
hyperæmia on release, a hyperæmia derived from the occlusion itself.   Two
groups have been heated and show reduced wheals, one of these has been
heated the longer and shows the smallest wheals ; the skin in both these
regions subsequently displays a heat hyperæmia, redness that extends to

WL3. *15° for 5 m.*

A

WL2. *43° for 1½ m.*

B   C

WL1. 43° for 2½ m.
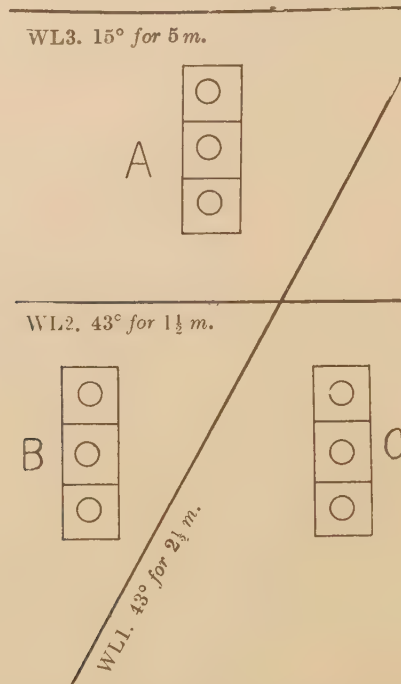
Fig. 31.   The squares are marked on the arm beforehand ; the circles indicate the points
subsequently punctured.   W.L. = water line.

the old water line, while the wheals are developing.   Apparently therefore
groups *B* and *C* are submitted to like influences throughout, except that
during the occlusion group *C* is heated the longer.

Experience shows, however, that the treatment may not be equal,
since the heat hyperæmia that appears after the release may be more intense
and long lasting in the skin of group *C*.   To obviate this difference as far
as possible,* the experiment is repeated step by step and the circulatory
arrest is subsequently maintained while all groups are immersed in cold
water at 13° to 16°C for an additional 5 minutes.   This cold bath prevents
the arm from developing more than a slight heat hyperæmia after it is

* It is impossible to obviate it entirely,(see page 148).

released, and renders more alike the conditions under which wheals of, groups *B* and *C* develop ; nevertheless the results are the same, full wheals appearing at *A*, reduced wheals at *B*, and *C* displaying much reduced wheals or none.

Thus it is shown that the reduction of the wheal in group *C* compared with group *B* is due to extra heating, *during the period of circulatory arrest* (*164*). That it is not due to difference in the condition of the skin at the release is shown by this experiment and by further observation ; for if the areas *B* and *C* are punctured with histamine, not before heating, but a little while before releasing the circulation, equal and prominent wheals appear over both areas.

Similar effects are also observed if, instead of hot water, water at 33° to 36° is used, though the reduction of whealing is less conspicuous ; water at these temperatures does not produce a subsequent heat hyperæmia.

Effect of cold. One minute after arresting the circulation to the limb histamine punctures are laid down in three groups ; group *C* is immersed for 5 minutes in water at 12° to 13°C, groups *B* and *C* are then immersed in water at 36° to 38° for 2 or 3 minutes, the arm dried and released. Wheals develop fully in group *C*, but are of reduced size in group *B*. That is so because, while group *C* was cooled, group *B* remained at room temperature. The wheals of group *A*, exposed to room temperature throughout, are intermediate in size (*164*).

A variation of the temperature experiments is to put down on the radial and ulnar surfaces of the arm, to which the circulation is arrested, two groups of histamine punctures. The arm is supinated and group *A* is brought under hot water (43°C), while group *B* is kept cool above the water by applying mops of cold water (18°C) to it, for 2 minutes. Both areas are now immersed in a bath of water at 18°C for 5 minutes ; the arm is then pronated and group *B* is brought under hot water for 2 minutes, while group *A* is kept cool. Both groups are then immersed in the 18°C bath for two minutes and, finally, in a bath at 37° ; while it lies in this the circulation is released and the development of the wheals is watched. At the end of the observation the two groups have been treated as follows :—

		A		*B*	
Circulation	43°	2 mins.		18°	2 mins.
	18°	5 mins.		18°	5 mins.
arrested	18°	2 mins.		43°	2 mins.
	18°	2 mins.		18°	2 mins.
Released	37°	until wheals develop fully.			

The two sets of wheals develop at the same rate and to the same extent. The experiment confirms the view that heat affects the reaction when it is applied and not through its after-effects on the released circulation ; these are distinct in the case of group *B*, while inappreciable in the case of group *A* (*164*).

To sum up, the circulation to the skin being stopped, wheals subsequently developing at the release are reduced in size, and this effect is assisted by high and is hindered by low temperature. The influence of temperature, exerted as it is during the period of circulatory arrest, forcibly suggests a chemical action.

Stroke wheals. If similar experiments are performed on skin that wheals to the stimulus of stroking, and the stroke is substituted for histamine, precisely similar effects are witnessed. The development of a stroke wheal, however, is more readily disturbed than is that of the histamine wheal by circulatory arrest and heating ; and lower temperatures and shorter periods of arrest, than those described for the corresponding histamine observations, must usually be employed (*164*).

Arising out of these experiments there are further observations now to be described and discussed.

Loss of increased permeability and the condition of refractoriness.

When a histamine puncture (or stroke) is laid down on skin deprived of its circulation and subsequently heated, the subsequent failure of whealing at the release is due to disappearance of the originally increased permeability of the vessel walls. The statement is made in this form because, if the release occurs earlier and before heat is applied, whealing promptly occurs ; it begins almost as soon as the circulation is restored, showing that the vessels possess increased permeability at the instant of release. In its time relations the development of wheals so produced contrasts with that of wheals produced on skin in which the circulation is free when the stimulus is applied ; here there is a latent period of $1\frac{1}{2}$ minutes or more, during which increased permeability is developing and its effects are becoming visible.

Thus, in the arm deprived of circulation and heated, the vessels affected by the stimulus at first develop the usual increased permeability, but, as the occlusion is continued, the vessel walls become less pervious. Now, it is impossible to attribute the failure of whealing to a simple decline of the vascular reaction, for, even when wheals fail to appear at the release, the full vascular dilatation is seen. Throughout the whole period of circulatory arrest, the purple spot remains in undiminished intensity on the skin and, as soon as the general hyperæmia following the release subsides, a full flare is seen around the area stimulated. Here is the additional and promised evidence that increased permeability on the one hand, and vascular dilatation on the other, are independent events. It is clear from this observation that local dilatation combined with reflex flare will not produce whealing ; increased permeability is separable from the rest of the vascular reaction.

When Grant and I (*164*) first noticed that histamine wheals fail to appear in the circumstances described, we thought that the poison might in the interval have diffused away or have been destroyed *in situ* ; but further observation and reflection rendered these conceptions untenable, for they are

inconsistent with the persisting vascular dilatation. They are particularly inconsistent with the appearance of a full flare at the release, and with the precise delay in its fading, a delay that, as stated, amounts to the period intervening between puncture and circulatory release. This has been described on page 87, but it is here to be added that the delay is similar and precise even though no wheals develop ; the statement likewise applies to the stroke reactions. The delayed fading of the flare is attributed to retention of histamine *in situ* ; the failure to wheal must be due therefore to change in the reactivity of the vessel wall in so far as its permeability is concerned.

The supposed irresponsiveness of the vessel wall to histamine can be put to the direct test by repuncturing the original points of skin with histamine. Two series of histamine punctures (Fig. 32, *A* and *B*) are laid down on skin deprived of its circulation. The arm is now heated for from 5 to 10 minutes

Once punctured   Repunctured   Control
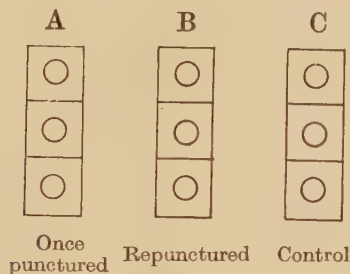
Fig. 32.

and subsequently cooled or, alternatively, is maintained throughout in a bath at 33°C for from 15 to 20 minutes. Immediately before releasing the circulation group *B* is repunctured with histamine and a fresh series *C* is laid down on neighbouring skin. The new punctures of *B* must be laid down precisely in the old places. After the release, little or no trace of whealing occurs in group *A* ; in group *C* wheals develop. In group *B* whealing is very slight ; although it may be somewhat greater than in group *A*, it is far less than in group *C* ; on some occasions it is so slight as to be imperceptible. Thus it is shown that areas, in which whealing fails on account of circulatory arrest and heating, will not wheal appreciably when histamine is freshly introduced. A lesser or greater degree of **refractoriness** has developed.

This relative refractoriness is not merely an apparent refractoriness, such as might arise if the minute vessels became clogged with blood cells during the period of circulatory arrest and if, as a consequence, the blood could not enter them at the release. The observation may be arranged, and has been arranged, in such a way that blood is seen to enter and flow in the vessels concerned at the release ; yet the refractoriness of the tissue is still displayed (*164*). It is ascribed therefore to an interaction between

the histamine introduced and the cells of the vessel wall that are concerned in transudation.

In our observations there is an obvious and close relation between refractoriness and the decline of previously increased permeability ; it is thought that both result from one and the same process. It is a chemical process that is in mind, since heat accelerates and cold retards it. Given that this conception is correct, and allowing that circulatory arrest with heating prevents the appearance of stroke wheals by a process similar to or identical with that preventing the appearance of histamine wheals, our theory would ascribe both to the interaction between a substance having a histamine-like action, or histamine itself, and the vessel wall.

If we are so far right, then it will follow that the skin of an urticarial subject, when rendered refractory to histamine, will fail to respond to a stroke by whealing ; and, *vice versa*, that, when a stroke wheal has been prevented from forming by circulatory arrest and heat, the line of stroke will prove refractory to a histamine stimulus. Now this is precisely what Grant and I found. If the skin of an urticarial subject is firmly stroked, and the arm is treated by compressing its main vessels and by heat, as in the corresponding histamine observation, no wheal develops at the release ; and, if histamine is punctured into the line of such a stroke, a little before or soon after the release, the line proves refractory or relatively refractory to it. A customary result is complete absence of whealing ; in some instances whealing is slight ; it is never so great as that which is produced by simultaneous control punctures on neighbouring skin.

The converse experiment is carried out as follows. In an urticarial subject, two small neighbouring areas are chosen and into each, while the circulation to the arm is arrested, six closely set histamine punctures are laid down, so that the affected areas may be sufficiently large. One of these areas is kept as a control because, if it subsequently wheals, the observation needs to be repeated. The arm is suitably heated and, at the release of the circulation, a firm stroke is drawn across the other punctured area. If the observation has been carried out successfully, the stroke yields a prominent wheal ; this wheal is broken where it crosses the area rendered refractory by histamine. The phenomenon is not always easy to display, because stroke wheals are very sensitive to interference and a sufficiently raised stroke wheal, in the circumstances of the observation, is not always obtained. The observation can be carried out only in subjects in whom fairly prominent wheals are produced by stroking, at the end of a period of circulatory arrest and heating that is sufficient to prevent histamine wheals from appearing ; it can be carried out only if the period of arrest and heating is of just the requisite length. Nevertheless it has been obtained unmistakably and repeatedly.

If a wheal is raised by stroking the back of an urticarial subject, the œdema eventually subsides ; during the later stages of this subsidence fresh stroke wheals that run across the old line are broken or reduced at the crossing points. This is a similar phenomenon, the old line

of stroke wheal having become refractory, or relatively so, to stimulation of the same kind.

These observations again demonstrate the parallelism between histamine and stroke wheals, and lead us to believe that underlying the formation of both there is a common chemical reaction.

When a small area of skin has been rendered refractory by stroking or by puncturing in histamine, and by subsequent treatment, the state of refractoriness does not persist indefinitely after the circulation is restored. Recovery begins about 5 or 10 minutes after the release, and is uninterrupted, though a varying time elapses before full whealing is again obtained.

To produce refractoriness heating is unessential, similar effects are to be obtained at normal arm temperatures (33°C); heat merely expedites the onset of the refractory state.

Moreover, arrest of the circulation is unessential; it may be regarded as merely displaying refractoriness by keeping fluid from exuding during the initial period of increased permeability. If the circulation is intact and the skin is stroked, a wheal develops and does not cease to grow until about 5 or 8 minutes have elapsed. These periods are not dissimilar from the minimal periods required for a stroked area to become refractory, when the circulation is arrested and the arm kept at its normal temperature. Thus, it is difficult to avoid considering refractoriness, and the relative impermeability of the vessel wall that accompanies it, as at least in part responsible for the ending of transudation, when wheals come to their full development in otherwise unmolested skin. In some part failure to develop further may be due to dilution of the liberated substance, in part it may be due to gathering pressure in the tissue spaces. The observation that circulatory arrest is unessential to a refractory state being developed, is supported by a fact already recorded, namely, that when stroke wheals on untreated skin are undergoing absorption, the affected area of skin presents refractoriness to further stroke stimulation.

Formation of craters. It has been stated that if histamine is punctured into an arm, the vessels of which are occluded, and the skin is heated long enough, wheals may subsequently fail to appear. When they do appear they are apt to do so in the form of miniature craters; that is to say, no whealing happens in the immediate neighbourhood of the puncture, but a small ring of œdema develops around the outer margin of the affected skin (*164, 250*). These craters are due to the interplay of refractoriness and diffusion. The histamine is put down centrally and it spreads, consequently the tissue first involved experiences the poison longer than does tissue that it subsequently reaches. The vessels of the central area become refractory and lose their permeability; the marginal vessels are less affected and transudation occurs through their walls.

A similar phenomenon is sometimes witnessed in the case of stroke wheals, similarly treated; two small ridges of œdema form along the parallel margins of the stroke, but the centre remains depressed.

The effects of simple heating on wheals reconsidered.

It has been said earlier in this chapter that, if skin to which the circula-tion is free is heated, whealing to subsequent stimulation is reduced or abolished. When seen in connection with histamine wheals, the effect was attributed to the exaggerated blood flow washing away the histamine before it has time to act ; and this conclusion seemed to be substantiated by observing that, if histamine is punctured into the skin a little before heat is applied, full or almost full whealing occurs. If this interpretation were valid, it would also be applicable to the similar phenomena in the case of stroke wheals, seeing that these behave similarly ; and the observations would thus provide another and powerful argument that a diffusible substance is liberated in mechanical injury to the skin and is responsible for whealing. As has been seen, however, heat applied to an arm in which the circulation has been arrested also prevents or reduces subsequent whealing, and it becomes conceivable that it acts similarly when the circulation is free, namely, by rendering the tissues refractory, and not by causing the removal of the irritant substance. If we are to use the effect of heat upon the naturally nourished skin to support the second conception, it becomes necessary to show that refractoriness of the skin, in the sense in which this term has been used, is not responsible.

The question is tested as follows :—The arm of a normal or urticarial subject is immersed in water at 44° to 45°C for 3 minutes, the circulation is arrested and histamine punctures (A) are laid down on the hot skin ; the arm is returned to the water and at the end of 1 minute the circulation is released ; more histamine punctures (B) are now laid down as a control, and the arm is again heated for 1 minute and then cooled in a bath at 16° to 18°C until wheals develop fully. The difference of treatment of the two histamine punctured areas and the end result may be tabulated.

A	B
Punctures laid down on hot skin.	Punctures laid down on hot skin.
1 minute of arrest and heat.	
1 minute of heat without arrest.	1 minute of heat without arrest.
Cooled.	Cooled.
Slightly reduced wheals.	Reduced wheals.

Area *A*, after being punctured, is subjected to heat while the circulation is arrested for 1 minute ; otherwise the procedures in the case of *A* and *B* are identical. Now, as we have seen, heat and arrest combined tend to render refractory the skin punctured with histamine. Area *B* possesses the advantage of escaping this influence. On the other hand, the histamine introduced into area *A* has lain in contact with the tissues, without the possibility of its being washed away, for 1 minute after its introduction. This advantage outweighs any that area *B* enjoys, and it results in the development of larger wheals at *A* than at *B*.

The experiment shows decisively that when histamine is punctured into an already heated skin, in which the circulation is free, the wheals developing

are reduced in size mainly because there is an increased circulation to the skin ; and we are able to return to the original explanation, namely, that the reduction is due to loss of histamine.

The same facts may be demonstrated in the case of stroke wheals, though, owing to their sensitiveness to heat, the result is less easily obtained. If the procedure described already is used, as a rule both series of wheals are reduced to mere traces. It is necessary to use lower temperatures and shorter periods of immersion, and the end-period of cooling, often unnecessary in the case of histamine, is here essential. The most favourable temperature and period are obtained by trial. In this manner important confirmatory evidence that a stroke liberates a chemical substance in the skin is obtainable.

In general agreement with the observations last recorded is the fact that if skin is stimulated when it is hyperæmic as a consequence of interferences other than heating, for example, if the stimulus is laid down on the flare that surrounds a previous stimulus, or on skin rendered hyperæmic by the release of an arrested circulation (reactive hyperæmia), a similar reduction of whealing is witnessed (*164*).*

Some differences between histamine and stroke reactions.

In our comparisons of histamine and stroke reactions, the remarkable similarity between them has stood forth constantly. In almost every particular these reactions are alike, they are similarly influenced by a variety of conditions. Such differences as have been found are quantitative, never qualitative ; and of these three are chiefly notable. The spread of the local vascular reaction in the skin during the period of circulatory arrest is normally greater in the case of histamine than is that of a stroke stimulus. Arrest of the circulation and heat combined affect the stroke wheal more profoundly than the histamine wheal. Lastly, a stroke wheal develops less prominently than does a histamine wheal, when the stimulus is laid down on superheated skin. The similarities of the two wheals are easy to understand if we acknowledge that, when the skin is stroked, a substance having a histamine-like action is liberated ; the same theory is competent to explain the differences. When the skin is stroked, the substance will be let loose uniformly and into every tissue space of the area ; when histamine is punctured into the skin the dose is concentrated at a point. The three differences noted can all be explained with reference to the distribution of the active substance. Thus the spread of the vascular reaction is attributed to diffusion. To produce a histamine wheal 4 mm. in diameter, sufficient histamine must be introduced on the needle to spread in adequate concentration for 2 mm. in every direction. In the case of the stroke, the concentration is presumably sufficient to produce whealing on the line of stroke

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* A reaction contrasting with that described in a footnote to page 79.

only. Similarly, when arrest of the circulation affects the subsequent size
of the wheal, fixation of the substance by the tissues will occur more readily
in the case of the stroke, because the substance is everywhere in dilute
solution and its contact with tissue elements is from the first more intimate.
Lastly, when the stroke is applied to the heated arm, the substance is
liberated diffusely over a large area and all the vessels of this area are involved
in its removal ; in the case of histamine the dose diffuses gradually from a
small central reservoir, and in the first stages of its removal fewer vessels
will take part.

     To sum up this chapter, the effects of temperature, combined or uncom-
bined with arrest of the circulation, strikingly confirm the previous con-
clusion that histamine and stroke reactions are fundamentally alike, and that
the last is due to the liberation of a substance having a histamine like action.
The same observations lend additional and convincing support to the
conclusion that increased permeability of the vessel wall is a reaction
separable from vascular dilatation.

Chapter VIII.

THE CONCENTRATION AND ORIGIN OF THE SUBSTANCE LIBERATED BY INJURY ; THE NATURE OF SKIN DEFENCE AND ITS CORRELATION WITH SHOCK ARISING OUT OF INJURY OR ANAPHYLAXIS.

The concentration and origin of the substance liberated.

THE evidence brought forward in previous chapters seems sufficient to establish the conclusion that injury of the skin liberates a substance exerting a local action indistinguishable from that of histamine upon the cutaneous vessels and nerves. Yet the evidence would be even more conclusive could such a substance be recovered and could it be shown that it is capable of whealing fresh skin when reintroduced. If the fluid collected in the stroke wheal is gathered and reintroduced into the skin, its effects are indecisive from this standpoint. Sometimes whealing is seen to follow, more often the result is negative (*164*). In so far as the positive effects are concerned, these, being inconstant, may not be emphasised ; neither may the negative effects be stressed. Until we are able to judge the quantity of substance liberated, we cannot gauge the degree to which it is diluted by the fluid poured out from the vessels. Though liberated in a concentration more than adequate to produce the effect witnessed, subsequent dilution may be conceived to rid it of this potency. The effects of histamine, when this is pricked into the skin in a dilution of about 1 in 500,000, are just distinct (*164, 229*). The effects of puncturing the skin through a solution of lower concentration than 1 in 1,000,000 are indistinguishable from those following a puncture through saline. We may say, therefore, that if such whealing as is produced by puncturing wheal fluid into the skin is produced by substances in the wheal fluid, then, expressed in the equivalent terms of histamine, the dilution of these substances is approximately 1 in a million.

In the hope of throwing further light upon the nature of the substance and its concentration in the skin, Grant and I (*164*) engaged in a long series of experiments that tested the reaction of the guinea pig's uterus to fluid

obtained from wheals of the skin resulting from stroking, or from small
blisters produced by burning heat. We found that these fluids stimulate
the uterus to strong contraction, as does histamine in very great dilution
(Dale and Laidlaw *56*). Using this method, the strength of active sub-
stances in the fluids tested was estimated, in terms of histamine, to be 1 in
1,500,000. We were, however, unable to use our results in support of our
hypothesis, because we could not obtain, from the same subjects and by
similar methods, blood plasma that would constantly yield smaller uterine
contractions or no contraction. In a sense, our control observations failed
us ; although they left us with the definite information that the fluid contains
a substance that like histamine contracts the uterus, yet it was found impos-
sible to exclude blood plasma, as opposed to the cellular structure of the
skin, as its source. This method of approach might profitably be explored
again.

Recently Miss Harmer and I (*169*, *170*) have studied the problem in a
different way. In preliminary studies, Harmer and Harris (*106*) determined
the effects of small subcutaneous doses of histamine upon the general circula-
tion of man ; a dose of 1·0 cc. of a 1 in 3,000 solution yields a general flush
of the skin, a rise of its temperature of 1°, 2°C or more, a small decline
of systolic, a greater decline of diastolic, pressure and an appreciable rise
of pulse rate. The flush is most conspicuous in parts of the skin that are
previously red. When smaller doses are used it is found that 0·2 cc. (0·06
mgr.) causes perceptible flushing of the face and a distinct rise of tempera-
ture (usually 0·5°) of the skin generally. The reaction to such doses is usually
too slight to be accompanied by any distinct fall of blood pressure or by a
very appreciable rise of pulse rate. We chose cases of urticaria factitia and
watched for similar general reactions after stroking and whealing consider-
able areas of the skin of the trunk. The facial flush and general rise of
cutaneous temperature were witnessed in each, and a small fall of blood
pressure in more than one of the subjects used.

These effects were compared with those produced by minute subcu-
taneous histamine injections, to which the urticarial subjects are no more
susceptible than controls ; the evidences of vasodilatation, when equal in
degree, were strikingly similar in duration and distribution. The facial
temperature begins to rise in 2 or 3 minutes, comes to its height in about
7 minutes and returns to its original point in about 12 to 20 minutes.
Control subjects similarly treated by stroking failed to manifest the
reactions.

These observations seem to present quite unequivocal evidence that a
vasodilator substance is released in the skin of susceptible subjects when this
is stroked ; and from the similarity of its general action with that of hista-
mine, its histamine like nature is again strongly suggested. Using this
method and computing roughly from the size and extent of the wheals the
amount of fluid transuded, we estimated the dilution of the substance in

this fluid to be about 1 in 1,500,000 in terms of histamine. The several estimates are thus in fair if not close agreement.

However we approach our problem experimentally, the resemblance between the reaction produced by the liberated substance and by histamine itself, seems clear or most suggestive.

If we had to deal with the skin reaction alone, we should be in a position to speak of the substance liberated as having a "histamine like" action; but the same statement would be true if we substituted "atropine like" or "morphine like" action, for both these substances produce the skin reactions described. The additional observations, in which it is shown that the effects of the released substance upon the general circulation again resemble those of histamine, give histamine a special significance; it is further to be observed that histamine stands out in contrast to other substances that possess an irritant action when introduced into the skin, in virtue of the high dilution in which it proves potent. Moreover, histamine is a protein derivative, it is extractable from animal tissues, as Barger and Dale (*10*) and more recently Best, Dale, Dudley and Thorpe (*20*) have shown (see page 234). Here it may again be emphasised that refractoriness of the vessels, ascribed to a chemical process, is produced by and exhibited to both histamine and the substance liberated by injury.

When these facts are coupled with observations in which it is found that the action of larger doses of histamine, introduced into the general circulation, produce profound effects of a very similar kind to those witnessed in extensive injuries of the tissues, observations presently to be described, then we are still more warranted in suspecting that the tissue substance liberated is a histamine like body or even histamine itself. A final conclusion that histamine is actually the substance released would be justified fully perhaps only if this substance had been recovered from the tissue spaces in injury and actually identified.

To maintain, for the moment, the reservation that histamine is still not finally proved to be the substance liberated in tissue injury, especially to meet a possibility that more than one substance is sometimes concerned (see page 129), and at the same time to avoid using the cumbersome phrase " a liberated substance or substances having a histamine like action," I shall speak of an **H-substance,** and in using it shall mean *any substance (or substances) that is liberated by the tissue cells and exerts on the minute vessels and nerve endings an influence culminating in the triple response.* The term will be used without inferring, more than has already been inferred, that we have to deal, in all instances in which an H-substance is under consideration, with a single substance having an invariable chemical constitution.

The question as to whether or not this substance is histamine itself is further discussed in Chapter XVII.

The vascular defences of the skin.   Inflammation.

Our main conclusions as to the mechanism underlying the skin's vascular defences have been in large part formulated. In Chapter VI, I have concluded that the skin responds to mechanical, thermal, electrical and chemical stimuli in one way, namely, by liberating a common chemical substance, and that this substance is directly responsible for the complete reaction as we see it. Further and weighty evidence in support of that conclusion has now been discussed, and we have been brought even to consider the nature of this substance. We may now reformulate our general law (page 90) and state that *whenever the skin displays an acute reaction in the form of the triple response this reaction is provoked directly by our H-substance.*

There exists in the skin a highly organised mechanism of defence against injuries, the defence summed up in the term **inflammation.** Although this term was originally used, as its derivation suggests, to cover just those processes that are considered in this book, namely, *redness*, *heat* and *swelling*, this definition has long been superseded ; the term has become more comprehensive, being now used to include processes other than those of vascular response. With these I have no concern in the present monograph, neither do I wish to infer that they have, or have not, the same fundamental underlying cause as have the vascular manifestations.* It is for this reason that the word inflammation has been avoided. The relation between the vascular defence and other defences remains for further investigation. I deal with the former only.

The agent that alarms the garrison and mobilises the first or vascular defences is a chemical agent derived from the tissues. The perfection of this mechanism is such that the defence is organised immediately and at every threatened point ; it is arranged and carried through locally, being independent of higher systems of control (nervous) and of distribution (cardio-vascular).

The tissue elements responsible for released substances.

I believe that the cells mainly responsible for the release of the H-substance and for the consequent vascular reactions of the skin are the living epidermal cells. The shortness of the period of latency is incompatible with the diffusion to the vessels of substances from any cells that are not their close neighbours. The horny layer is readily excluded, for punctures or cuts confined to this are followed by no reaction. On the other hand a needle-prick that is just sufficient to penetrate through the horny layer and to reach the living epidermis, always yields a vascular response. Thus, a prick just sufficient to produce a painful sensation is always followed by a reaction.

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* In two interesting papers Wolf (*267*, *268*) concludes that histamine has a strong chemiotactic action and causes leucocytes to wander out of vessels to which it is applied. Bloom (*25*), however, has come to a contrary conclusion.

Under the binocular microscope a fine needle may be passed into the skin between neighbouring capillary loops ; that is to say, it is made to penetrate the epidermal layer where it is at its thickest, between the adjacent papillæ of the skin ; it is passed in until its sharp point is felt, and the point is then seen to lie at or very near the level of the tops of the capillary loops. The needle does not penetrate nearly to the true skin or to the subpapillary plexus ; thus injury in the true sense is confined to epidermis ; in these circumstances a vascular reaction is always seen subsequently. Without doubt the epidermal cells are those chiefly injured when the various forms of stimulus previously described are employed. They are the first living cells to receive the stimulus of heat, they are the first to become frozen, they bear the brunt of mechanical and electrical stimulation. They frequently show subsequent signs of having been injured ; all the stronger forms of stimulation, such as the burn and the freeze, are followed by desquamation of the skin. It is not until forms of stimulus far stronger than those here described are employed that deeper layers of the skin are killed, leading to necrosis or ulceration and to thrombosis of vessels.

That the substances are not released mainly from the endothelial walls of the minute vessels of the skin is indicated by the fact that these show no subsequent evidence of damage ; after the skin has been frozen sufficiently to form a conspicuous wheal, and this has subsided, the capillaries are found to be intact and carrying blood ; thrombosis does not occur in them. Another argument against the view that the substances are mainly released from the endothelium is that it is impossible to induce even by very slight injury a lasting dilatation of the capillaries of the arm, while the venules of the more deeply lying and protected subpapillary plexus remain uninvolved. It is clear that, if injury to the epidermal layer of skin is responsible, then the released substances will be spread uniformly, and will affect capillaries and venules together and uniformly ; that is what actually happens.

It should be made clear, however, that in placing the responsibility for reactions such as are here described mainly upon the epidermis, contributions from other cellular elements cannot be excluded. It is impossible to exclude either the living cell of the vessel itself, or the cells of the cutis vera. It would certainly be a mistake to regard a particular form of cell as alone capable of yielding the released substances ; it is only possible to say that we look to the epidermal cell as chiefly contributing to reactions that produce superficial cutaneous vasodilatation and whealing. In speaking in future of the *skin cells* as those from which the substances are released, I shall have the epidermis particularly in mind, but subject to the reservations here stated.

This monograph deals with vascular reactions of the *skin* ; it is not within its scope to examine at any length similar reactions of the deeper lying tissues. There is no doubt, however, that these occur ; thus, in so far as injury to subcutaneous tissue is concerned, there is no reason to believe

that its reactions are essentially different. When mechanical injuries go more deeply than the skin, hyperæmia and outpouring of fluid are evidenced by the rise of temperature and swelling in the bruise. Similar effects occur when histamine is injected into the subcutaneous tissues. Though these reactions have not been explored in any detail, it is clearly probable that similar agencies are here at work, and that the skin does not stand alone in exhibiting the phenomena described. The reactions are almost certainly similar in most of the body tissues, for bruising of the viscera yields hyperæmia and œdema, as illustrated in the effects of firm strokes described by Ebbecke (75) and by surgical experience ; Dale and Richards (59) have demonstrated that histamine when painted on the pancreas has similar effects.

The reaction of an organ such as the spleen or liver differs in one respect only according to Ebbecke, namely in the absence of a surrounding flare. Florey (85) likewise saw no surrounding reaction, but only a local one, in the case of the cortex cerebri. The reactions of the cerebral vessels, however, seem in other respects peculiar. Thus Florey has been unable to obtain, with any regularity, dilatation of the superficial cerebral vessels in response to mechanical stimuli, and iodine is found to yield, as a preliminary reaction, contraction and not dilatation. It might be suggested that the peculiarity of these responses is due to an absence of the particular cellular elements that may be supposed responsible for the liberation of our H-substance in injuries to the skin ; but Lee (148) believes that histamine itself is without effect on the cerebral capillaries.

Histamine and traumatic shock.

There are certain general effects that recently have become more clearly understood and that arise out of tissue injury in the broad sense ; there are also certain general effects of the substance histamine when introduced into the circulation in comparatively large doses. The comparison of these effects furnishes further evidence that our H-substance is liberated in response to injuries. It is appropriate, therefore, here to consider them and thus to link up the purely local reaction with more profound influences upon the body as a whole.

Histamine shock. The work of Dale and his associates Laidlaw and Richards (55 to 59) upon histamine, and the suggestions arising out of their observations, have placed this substance as a type in the forefront of the discussion, and have led to a searching comparison of both its local and general effects with those of tissue injury.

When histamine is injected intravenously into cats in doses of 1 to 2 mgr. per kilogram of bodyweight, its almost immediate effect is to produce contraction of unstriped muscle elements ; this manifests itself in respiratory distress that is due to contraction of the bronchiolar muscles, and in a rise of blood pressure that is due to contraction of the muscle of the arterioles. Very soon the main phase of the action sets in, and this is displayed by a

continuous fall of blood pressure, which becomes profound within 4 or 5 minutes of the injection. The heart continues to act vigorously and its failure is not the cause of the decline of pressure ; nor is the cause arterial dilatation, on the contrary these vessels appear to be constricted. The heart, the arteries and even the veins, which are seen to be more or less flaccid, are relatively unfilled, the liver is pale and this organ and the spleen undistended. When search was made for the missing volume of blood, it carried these workers to the smallest vessels. In the first place the blood remaining in the vessels presents a concentration of red blood cells, indicating by its increase a conspicuous loss of blood plasma and by inference an œdema of the tissues ; secondly, there is often visible evidence that the minute venules of the bowels are greatly distended. Further and more direct observation led the same workers to conclude that histamine, when injected intravenously, constricts the arteries and arterioles, but has a direct and powerfully dilating effect on the smallest vessels. Their hypothesis of " histamine shock," as they term it, is that the circulation of blood is brought to a precariously low point by depletion of the central vessels, much richly corpuscular blood remaining locked in the minute vessels and much of its fluid part finding its way into extravascular tissue spaces.

The constrictor effect on the arterioles in the cat does not appear in the dog. In this animal and in the monkey, as Burn and Dale have shown recently (37) the arterioles certainly relax ; evidence of a similar action of small intravenous or subcutaneous doses* given to human subjects has been brought forward from my laboratory by the simultaneous observations of Harmer and Harris (*106*). Thus, in man and the last animals named, the relaxation appears to extend farther up the arterial tree from the capillaries than is the case in the cat ; otherwise the action of histamine on the cardiovascular system is similar in the two species. The most important reaction, namely, that of the minute vessels, seems universal in mammalia ; that is so even for the rabbit, as has recently been shown (*172*).

Inchley (*122*) emphasises a constrictor action upon the veins and venules ; he believes that this holds up the blood in the capillaries and is responsible for shock. That histamine exerts a constrictor effect on the muscular veins may be acknowledged, but it has no such action on the venules of the skin, which according to Spalteholz (*231, 231a*) are almost completely endothelial ; here the direct dilator effect of the substance on the minute blood vessels is undoubted, for it is limited to the minute vessels that come into actual contact with histamine introduced. Considered from a more general standpoint, Inchley's experiments do not convince that venous constriction plays so important a part in filling the minute vessels as does active dilatation of the minute vessels themselves. These form a large potential reservoir, and into this reservoir when it is opened, the blood of the body is supposed to drain.

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* Larger doses (6-8 mgr.) produce in man a conspicuous fall of blood pressure, respiratory distress, contraction of the stomach and occasionally collapse, as Schenk and workers cited by him have shown (*222a*).

Wound shock. It has long been known that, as a secondary effect of severe lacerating wounds, or surgical operations, patients present a condition of more or less profound collapse, in which the pulse is rapid and indistinct and the blood pressure greatly depressed ; the skin is pale, but may be cyanosed. This state has been the subject of numerous experiments on animals, in which similar tissue injuries have been created deliberately under anæsthetics. These experiments, and the intensive studies of shock in man and animals during the period of the war, revealed the cause of lowered blood pressure in diminished cardiac output ; and they have led to the belief that the output declines because the blood in circulation is decreased, a decrease accounted for in part by a loss of blood plasma and in part to blood being retained in the smallest vessels (Sherrington and Copeman (*227*), Mann (*184, 185*), Cannon (*40*) and others).

Reduction of the total blood and plasma volumes in circulation in the collapsed patient was actually found by Keith (*128*). Thus striking resemblances, of which the chief have been described, have been established as existing between wound- and histamine-shock. Evidence that absorption of products from the damaged tissues plays a large part in bringing about traumatic shock, finally appeared in the clinical observations of Quénu (*207, 208*), who cited cases to show that shock may be promptly relieved by removing the lacerated tissues, and that the onset of shock is related, in the case of a wounded limb to which a tourniquet had been applied, to the release of the circulation to the damaged tissues ; and in the later but independent animal experiments of Delbet (*62*), Cannon and Bayliss (*14, 42*). The first experimenter found that extracts of antolysed muscle produce a condition simulating shock on injection, and the last workers demonstrated that the usual fall of blood pressure, following deliberate injuries, is postponed during obstruction of the circulation to the damaged tissues.

This brief description of histamine- and wound-shock will suffice to set forth the salient features of an extremely important series of observations, in regard to which fuller details and comments will be found in recent writings of Dale (*55*) and Cannon (*41*). Without wandering far from the main thesis of this monograph, I am able to display the relevance of observations upon simple skin injuries to the more generalised effects of severe injuries, and to attempt briefly to place them in perspective in the following paragraphs.

Review of local and general reactions.

Reactions to the type substance histamine. When introduced into the skin in minute quantities, this poison produces a characteristic series of independent phenomena comprising (*a*) local dilatation of the minute blood vessels by a direct action upon them ; (*b*) a widespread dilatation of neighbouring strong arterioles through the medium of a local reflex mechanism ; and (*c*) increased permeability of the vessel walls by direct action. This

series of phenomena may be termed the type reaction, and it leads to manifest œdema of the skin.

When histamine finds its way into the general circulation its main action is very similar, but it is widespread, producing a general dilatation of the minute blood vessels and a consequent depletion of the main vessels and the heart; this depletion is exaggerated by the action of histamine in rendering the vessel walls more pervious, whereby plasma passes out into the tissue spaces. Manifest œdema of the tissues is not evident in general histamine poisoning, neither is it evident in wound shock. Recent observations by Drury (*68a*) in my laboratory show that manifest œdema of the subcutaneous tissues of the leg does not occur until the volume of the limb has increased by about 10 per cent. If the whole blood plasma were to pass into and become uniformly distributed in the tissue spaces, œdema as determined by pitting of the tissues would not be manifest, for there is not sufficient plasma in circulation to produce such œdema, which can come only gradually and by accumulation.

Reactions to injury. When the skin of a susceptible subject is stroked, when the normal skin is repeatedly stroked or suffers a single and more severe mechanical injury, the type reaction follows locally, is displayed in all its details and leads to œdema of the skin. A similar reaction is produced by minute lacerations of the skin such as follow a scratch with the point of a needle. These reactions to injury are ascribed upon independent evidence to the liberation of H-substance in the skin. Widespread stroking of the skin in subjects that wheal, induces the beginning of a general reaction similar to that produced by minute intravenous doses of histamine (*169, 170*).

The accumulated evidence certainly suggests strongly—I think it may be said to prove—that extensive and severe mechanical injury of the skin and more deeply lying tissues will liberate our H-substance in greater quantity and that this, being absorbed into the general circulation, will induce symptoms similar to those of the secondary wound shock by dilating the minute vessels and rendering them permeable.

Reactions to scalds and burns. A mild scald of the skin is followed by the type reaction and leads also to œdema of the skin. These events are likewise attributable to the liberation of the H-substance locally.

More extensive burns give rise to a secondary and dangerous state of shock, and this has been suspected for very many years to result, at all events in large part, from the absorption of toxic substances. This is the view accepted by Bardeen (*7, 8*) and by Robertson and Boyd (*219*); the last workers have recovered from burnt skin substances that, when introduced into a healthy animal, induce a condition resembling shock.* In this connection I think it notable that Underhill and Pack (*253*) find the hæmoglobin

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* Recently indeed the treatment of superficial burns in man by excision of the damaged tissue has been attempted (Willis *266*).

percentage in blood to be greatly raised in severe burns ; the red blood cells are concentrated in consequence of loss of blood fluids.*

It is difficult to pass in review the series of statements contained in these last few paragraphs without being impressed by the manner in which they are in process of becoming harmonised into a co-ordinate and simplified whole.

From the simple response of a healthy skin to such stimuli as are experienced daily by almost all ; through the more severe though still trivial local injuries, the bruise, the blister arising from friction or corrosive fluid, and the small scald, which find their simple household remedies ; to the most grave effects of mechanical injury and severe burning, which in their later manifestations endanger life, we pass by simple transition. It becomes apparent that this transition is one of quantity and not of quality ; underlying the whole series there is seemingly one determining cause, the unvarying reply of the affected cell to injury. This response of the cell or of a small group of cells protects locally, but when it is accompanied by a like response of multitudes of cells, a massive action results, and this soon threatens or terminates the life of the organism as a whole. The instance is one in which the action of the individual, or of a group of individuals, though purely defensive of self or of local interest, helps to jeopardise the safety of the whole community of which it forms a part.

Anaphylaxis and related phenomena.

When a foreign protein, such as egg albumin, is injected intravenously in a suitable dose, it gives rise after a time, as is now well known, to a susceptible state ; this susceptible state is one during which a further dose of the same substance yields a severe or fatal form of acute poisoning or anaphylaxis. The symptoms of anaphylactic shock, as it has come to be known, vary in different animal species ; thus in the guinea pig they are attributable in chief part to contraction of the unstriped muscle fibres of the body, especially those of the bronchioles, while in other animals they are attributable chiefly to poisoning of the small blood-vessels and to consequent circulatory collapse.

The resemblance between these reactions and those produced by the injection of crude peptone was pointed out by Biedl and Kraus (*21*).† Dale and Laidlaw (*56*) remarked in an early paper of their series upon the similar effects produced by histamine and, in a later publication (*58*), emphasised the similarity. The resemblance in detail is found to be remarkable, not

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* They attribute this loss, on grounds that are not clear, solely to loss of fluid through the burnt surfaces.

† Amongst many other resemblances they remark that in both states the polymorphonuclear leucocytes disappear almost entirely from the blood and that adrenalin fails to produce recovery of blood pressure ; the loss of polymorphonuclear cells occurs in histamine shock also (*58*).

only when a given species is considered, but when the comparison is extended to species in which the prominent group of symptoms varies in its type.

Phenomena now commonly regarded as anaphylactic in origin are also seen in man, the best example being perhaps the reaction to a repeated dose of antidiphtheritic horse serum. In man chief manifestations are asthmatic distress and phenomena attributable to damage of the vascular system, prominent amongst which is the familiar serum urticaria.

It is known also that many people display extreme susceptibility to certain protoplasmic substances; that a minute dose of pollen extract, of egg, or of fish extract, will induce, in the correspondingly susceptible, attacks of asthma, urticaria and eventually signs of collapse. That these manifestations are brought about also through a mechanism similar to that involved in animal anaphylaxis is open to little doubt, though the manner in which susceptibility is acquired remains unknown. In anaphylaxis, the seat of poisoning, as Dale (*54*) has shown, is in the reacting tissue cells; according to his view the reaction is due to the union of the poison introduced and the special protective substance, or immune body, previously present in these cells and formed there as a consequence of the first or sensitising dose of poison. If a minute quantity of the specific poison is pricked into the skin * of a susceptible person, a local urticaria results; a response that is now widely used in searching out the specific susceptibilities from which particular subjects suffer. The remarkable similarity between the reaction to intravenous injections of histamine and anaphylactic shock has been stated; the presence of the cutaneous response in susceptible human beings permits the further and more detailed comparison of the local anaphylactic response, with the loca' response to histamine. Here again notable agreement is found.

Grant and I (*166*) studied for this purpose a patient showing susceptibility to fish. The case was of a familiar kind; a general urticarial eruption followed the ingestion of a mouthful of fish. The man could not tolerate the boiling of fish in his house, since it provoked similar though less serious attacks. We compared the effects produced by pricking histamine, to which his reaction was normal, and a suitably diluted extract of fish simultaneously into a number of areas of this patient's skin; † the reaction to fish extract was similar to that of histamine in every respect; each produced local dilatation, surrounding flare, and whealing of precisely similar forms. The two reactions occurred almost simultaneously; they continued hand in hand. Similar results have been obtained by Hare (*105*), who, though using our

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* In routine tests for specific sensitivity it is the custom either to scarify the skin and then to place upon it the substance to be tested, or to inject the substance intradermally. These methods give no more satisfactory end results than that of pricking in the substance, and cause more inconvenience to the subject.

† The active substance appears not to be a coagulable protein, nor is it histamine; Dr. C. R. Harington regards it as associated with nucleic acid, and it gave in this subject a reaction equal to that of histamine 170 times as concentrated (*166*).

methods, worked independently of us and carried the comparison further than we did. Thus he showed that the histamine stimulus renders the skin refractory to the anaphylactic poison and that the latter stimulus renders the skin refractory to histamine ; this is an important demonstration.

The similarity between the histamine reactions and the anaphylactic phenomena, whether the general reaction, the local response, or both are considered, is abundantly clear ; it is so clear that a single fundamental cause must inevitably be postulated to explain the two. There are alternatives ; it may be suggested that anaphylactic poisoning liberates H-substance and that the response as we see it is the result of this liberation (local or general) ; or it may be suggested (Dale and Laidlaw *58*) that the histamine affects the reacting cells by producing in these a physical change, of a kind identical with that produced in them when stimulated in anaphylaxis. That a common physical change in the reacting cells is an end result in the two instances is not in doubt ; in both instances the cells react similarly, by contraction in the case of unstriped muscle, by relaxation and increased permeability, separable phenomena be it noted, in the case of the endothelial cell layer. The first view would ascribe this change to a single cause, namely, to the presence of histamine or H-substance. The second view regards the physical change in the cells as the common end result either of their interaction with histamine, or of the interaction within them of antigen and antibody. For such coincidence of reaction there is no clear explanation. The relative simplicity of the first view is in its favour ; certain further considerations also bring it support. The effect of histamine and that of anaphylaxis may be identical on the cell of the vessel wall ; each may, as it happens, lead to one and the same colloidal rearrangement of its particles and thus to relaxation and increased permeability. This is all conceivable, though the conception is not facilitated by the dual character of the local vascular response ; it is even conceivable that a corresponding physical change in unstriped muscle may bring its cells to contraction ; but when we add to these effects, as we must, another, namely, stimulation of the nerve fibres of a local reflex arc, tissue of wholly different type, then the view that two distinct forms of stimulus produce these common and complex end effects, becomes most difficult to accept.

The two views applied to the reaction of cutaneous vessels are summed up in the accompanying diagrams. In the first diagram antigen is represented as playing on a sensitised cell, with the release of H-substance and the subsequent and usual actions that this body exercises directly on vessel wall and nerve ending.* In the second the antigen is supposed to act directly upon the tissue elements that respond, and in so doing to reproduce precisely the effects of histamine upon these. It is to be stated that while the first view

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* The mechanism of the reaction between antigen and a sensitised cell and the desensitisation of this cell by the reaction, does not here concern us. This problem is a side issue, as is the sensitisation of the skin to light by hæmatoporphyrin.

postulates a less direct action of antigen, namely, a preliminary stimulation of a cell, which then releases its H-substance, it is not intended that this view should exclude the idea that the class of cell that is supersensitive to such stimulation is of a distinct order to those ultimately responding and producing the anaphylactic symptoms ; for example, in the case of skin, we cannot exclude the release of H-substance from endothelium. The second view seems definitely to imply that the cell attacked by antigen and that which responds are always one and the same.
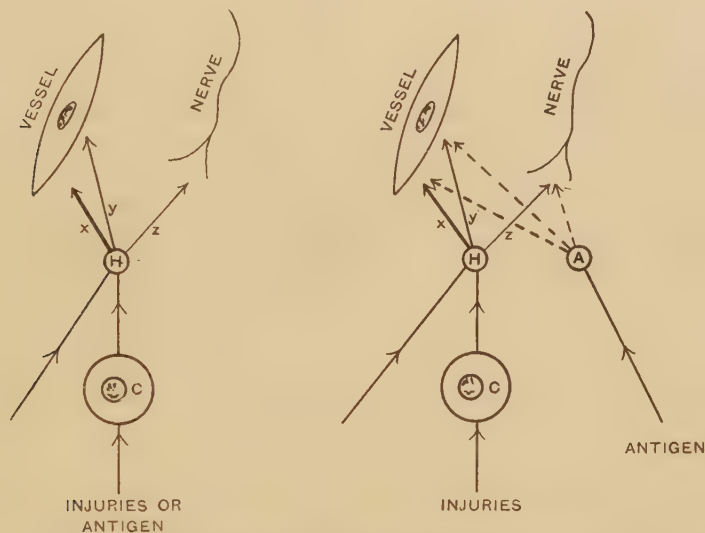
Fig. 33. A diagrammatic representation of two views of the anaphylactic reaction, as this occurs in the skin, correlated with the reactions to injury.

Injuries are represented as acting on cells (*c*) in the skin. These liberate the H-substance (*H*). Such a substance has three actions upon the blood vessels ; it dilates the minute vessels (action *x*) and increases their permeability (*y*), it acts on the local nervous mechanism producing reflexly an arteriolar dilatation (*z*). According to the first view discussed in the text the anaphylactic reaction is also brought about by injury to cells in the skin, whereby the H-substance is liberated and proceeds to act in its accustomed manner (left-hand diagram). According to the second view, the anaphylactic poison when introduced directly calls forth the triple reaction (*x, y* and *z*) in all its detail (right-hand diagram).

If, in considering the alternatives, we start with the phenomena of general anaphylaxis, we review a series of phenomena, of which the chief seem to be contraction of unstriped muscle, dilatation and increased permeability of the small vessels. The reaction is admittedly of an artificial kind, being produced by many substances that never can find their way naturally into the circulating blood ; the end result shows no purposive quality ; it is seemingly purely perverse and inimical to the tissues themselves and to the organism.

If on the other hand we start by considering the local reaction to injury, the facts link themselves together in a more orderly manner. Here is a

complex mechanism, comprising two separable and direct effects on the vessel wall, a third and independent effect, produced through nervous channels and at a distance ; this triple response is purposive, being directed to the tissue spaces and producing local changes in blood supply and lymph flow requisite to defend the surviving cells from further injury. This increased flow will tend to wash away or dilute injurious substances and will bring leucocytes more quickly through the vessels of the affected region ; very possibly it acts further as a necessary preliminary to reparative processes ; thus, essentially it is a protective mechanism that is normally called into play daily or hourly. Interpreted on these lines local anaphylaxis becomes but one more example of cell injury and its associated response. In general anaphylaxis, the same local skin mechanism is set in motion ; the lines of defence, so to speak, are now attacked from the rear ; the counter-attack is delivered, ineffectively it is true, but in the manner and direction in which it has been prepared.

These considerations lead us to conclude that a fundamental factor in the anaphylactic reaction is the liberation of our H-substance,* a view also adopted by Hare (*105*).

* Here and previously in using the phrase anaphylactic reaction I am basing conclusions upon the phenomenon of so-called protein sensitivity. It is not universally accepted that this phenomenon is identical with the anaphylactic reactions that have become models in animal experiment (*273*), though it is certainly not to be doubted that it holds much in common with the latter. If the mechanism of the two reactions proves ultimately to be different in essence, the conclusion here put forward will become restricted to " protein sensitivity ; " for the moment it is given the wider application.

Related to the phenomena discussed are those in which the susceptibility of the skin becomes increased to irritant substances that are repeatedly applied to it; some of these are of simple chemical constitution. Amongst such substances is the well known instance of poisoning by primulaceous plants (Low *182*), by salvarsan, antipyrin, morphia, strychnine, potassium iodide, mustard oil and an almost countless number of other substances. Many curious clinical observations relating to this and allied problems have been collected by Low (*182*) and by Duke (*73*) and such are also discussed by Zinsser (*273*). The increased susceptibility to poisons applied is not merely local ; the whole skin tends to manifest it simultaneously, and instances are recorded in which it has been thought that the state may be transferred passively to animals ; a most interesting though unusual example of passive transference is to be found in a recent report by Lehner and Rajka (*153*). The mechanism of hypersensitiveness induced by repeated applications to the skin is incompletely understood, and its discussion would carry us far beyond the scope of this monograph. Actually the problem does not directly concern the manner in which the vessels respond, but concerns the way in which the H-substance becomes released in the skin, for I presume that increased sensitive-ness means an increased tendency of the cells to release this substance, when suitably stimulated, and does not indicate an increased reactivity of the vessels themselves. In the last connection, however, the recent observations of Török, Lehner and Urbán upon the response of the skin to repeated injections of histamine should be studied (*248*).

CHAPTER IX.

THE SLOWER REACTIONS OF THE SKIN TO ULTRAVIOLET LIGHT AND TO SOME OTHER FORMS OF STIMULATION.

In Chapter IV the action upon the skin of a number of irritant substances has been considered, and it has been shown that these all produce an acute reaction having almost or quite constant time relations and other characteristics. It has been pointed out that all these irritants are such as quickly stimulate or actually kill living cells; from the time relations of their reactions they must liberate the H-substance almost instantly. The poisons in question act, according to this view, in a manner quite comparable to that of mechanical, thermal and other physical stimuli.

There are other forms of stimulus that, acting sufficiently powerfully, prove inimical to life, but produce their effects more slowly. Discussion of these has been deferred to the present chapter. It has become, or in other instances it is becoming, clear that many familiar reactions of the skin that follow after considerable periods of latency, for example, the response to ultraviolet light and to irradiations of even shorter wave length, to bacterial toxins, to chemical substances of known constitution such as mustard gas, are to be interpreted in terms similar to those employed in explaining the acute reactions that have been more freely investigated and already discussed ; it becomes increasingly apparent that in the slower reactions the same mechanism of defence, dependent upon an intervening and natural chemical stimulus, is brought into play. Evidence bearing upon the slow reactions, and their correlation with the more acute, will be considered in the present chapter. For this purpose the illustration of ultraviolet light is first chosen.

Ultraviolet light.

Experience has long since familiarised man with the fact that exposure to the sun's rays will produce vascular and pigmentary changes in the skin ; that similar changes occur in response to powerful artificial light has naturally become known in recent times only. The clinician Charcot (45) appears to have been the first clearly to realise (in 1858) that the skin is stimulated, not by the heat, but by the chemical rays of sunshine. This conclusion was later fully substantiated by the experiments of Gintrax, Widmark (264), and of Finsen (83, 84), who tested the different effects of variously filtered light on human skin and other structures.

The vascular effects produced by sunlight and by the emanations of the mercury vapour lamp are very similar, and depend especially on ultraviolet rays having a wave length of approximately $300\mu\mu$ (Hausser and Vahle, *109*).

The susceptibility of the skin of different individuals to ultraviolet light varies a good deal. In large part this is due to difference in the pigment content of the skin, penetration being thereby influenced; relatively unpigmented skins receive a stronger stimulus and, as is well recognised, burn most easily. In part it consists of a variation in response to stimulation, a variation which is imperfectly understood but which may be compared with similar variations in the response to mechanical and thermal injuries of the skin. To such cases reference will again be made.

Reaction to short exposures. The usual reaction, following for example a 3 to 6 minute exposure of the skin of the forearm at 18 inches from a mercury vapour lamp, is reddening of the skin, which begins to appear in from 30 to 60 minutes and deepens during the following hour. The area of redness developed in this time corresponds precisely to the area of skin exposed (*83, 104, 175*). Though unaccompanied by any appreciable rise of temperature, an increased flow of blood to the reddened skin can be demonstrated by the congestion test (*175*). Microscopically all the minute vessels of the affected area are seen to be dilated, including capillaries, venules and terminal arterioles, when the last are visible (*175*). This reaction corresponds to the local dilatation of the minute vessels previously described in response to mechanical stimulation. If, with the circulation to the skin obstructed, the red skin is pressed upon and blanched, the colour returns to it at once when this local pressure is withdrawn. This fact and the exact restriction of the reddening to the skin exposed to the light stimulus, are sufficient to show that the local dilatation is active and not passive; for the appearances and behaviour of the reddened skin are precisely similar to those of skin reddened by other forms of stimulation. The long latency of the reaction prevents us from observing its development in skin to which the circulation is kept obstructed throughout, actually the most conclusive test of active as opposed to passive dilatation.

The vascular reaction is independent of a local nervous mechanism, occurring in skin to which the nerves have degenerated.

The last statement is made emphatically. If, as has indeed been stated, the contrary were true, the local reaction would be distinct in its mechanism from that to forms of cutaneous stimulation previously described. The position is as follows:—Moycho (*195*) in 1913 irradiated the ears of rabbits; sometimes the nerves to the ear were intact, sometimes they were all cut a short while before, sometimes a long while before, and sometimes after, the irradiation. In all instances the ear reacted, and the reaction of the denervated ear, whether denervated before or after the irradiation, began earlier, was more intense, but subsided more quickly. He concluded from these experiments and from his finding similar results upon increasing the temperature of one ear without interfering with the nerves, that the differences that are found are due to differences in the circulation to the ears. Dreyer and Jansen (*68*) are reported as having witnessed similar effects in the rabbit's ear after cutting the cervical sympathetic alone.

So far as the human skin is concerned, Dixon (*65*) states that if local anæsthesia is maintained for two or three hours, an application of ultraviolet rays is found to have lost most of its stimulant

properties and that the skin is but little affected. He concludes that the reaction is an axon-reflex. Sobotka (*228*) using similar methods, failed to obtain these results. We have investigated the matter further (*167*), using, not local anæsthesia, which produces too great a local reaction to be reliable (see page 69), but surgical section of peripheral nerves with recent degeneration. The anæsthetic skin of patients in whom cutaneous nerves have been cut during surgical operations, when tested by puncturing in histamine, and by other forms of injury, was found to display no trace of the true local reflex that manifests itself as a surrounding flare ; but the local effects of ultraviolet light on such skin were perfectly clear and definite. The local reaction was in two cases as intense and in one case somewhat less intense than upon control skin. These observations leave no doubt as to the non-intervention of an axon reflex in the main visible reaction.

Moycho believed that the effects of degeneration upon the visible reaction are to be explained by altered blood supply to the skin, though the precise manner in which such change is brought about is imperfectly understood. The change is in fact inconstant, not only in degree, but in direction. Thus, while Moycho found a more intense reaction in the denervated ear of rabbits, on the one occasion when we saw a distinct difference in man it was of the reverse kind. In this connection attention may be called again to Sobotka's work (*228*). He found that if the human skin is exposed to heat, or is reddened by other forms of stimulation, that this reddening may distinctly influence the reaction to ultraviolet light ; usually it intensifies the reaction, but, from time to time it diminishes it. Zotterman and I have repeated these observations with heat (unpublished observations) and can confirm Sobotka in both respects. In individual cases, or in one and the same case with separate tests, intensification or diminution of the light reaction is witnessed. It seems to us that, if these influences are the result of circulatory disturbance, there is no escape from the conclusion that an increased circulation rate influences the ultra-violet reaction in two distinct and opposite directions, and that these two effects are differently combined in different skins, or in the same skin from time to time. Thus, it might be suggested that an increased bloodflow, while increasing the rate at which the vasodilator substance is released, also increases the rate at which it is eliminated from the tissue spaces, and that the balance is not always struck at the same point. However that may be, vascular changes are certainly associated with differences in the reaction, and this is true, as Sobotka states, not only of the ultraviolet reaction but also of the reaction to other forms of cutaneous stimulation, such as the stroke, X ray emanations, etc.. In so far as the local response to stroking is concerned we confirm his observations, and also that this may be intensified or may be diminished by heating. The matter is evidently a complex one, but it is manifest that slight differences of reaction in skin, in which there is reason to suspect previous circulatory disturbance, may not justifiably be accounted for on other hypothetical grounds until this factor has been eliminated.

Referring again to the reaction of the denervated skin to ultraviolet light, I am inclined to agree with Moycho that previous change in its vascular supply may influence the reaction, but would add that a second possible source of interference is the cutting off of natural trophic influences (see page 235).

To resume, the local reddening, while usually well defined within an hour, continues to brighten for a further hour or more, when the colouration is usually at its deepest. On the following day, or the day after, the skin is a little swollen as well and is usually tender in greater or lesser degree. This swelling subsides within a day or two of its appearance. Such is the vascular reaction to short exposures and this is its usual description (*83, 104, 175*).

There are, however, some important additional phenomena, recently described by Zotterman and myself (*175*). Sometimes as early as 4 to 8 hours after the exposure, more usually after a longer delay, the area of redness is noticed to have extended slightly. The extension increases and in 20 to 24 hours has spread usually 2 or 3 millimetres beyond the margins of the area exposed. The margins now lack their original crispness, they are less defined and often slightly irregular in contour.

This spread is readily demonstrated by shielding the skin during the exposure by means of a piece of black paper, cut in the form shown in Fig. 36*a*, page 125. The shield consists of a black triangle 18 mm. long, supported by a short stem 2 mm. broad ; the triangle is surrounded by slits, 2 mm. broad, through which the light falls on the skin.

When, after exposing the skin through this shield, the ultraviolet reddening becomes defined, it has precisely the dimensions of the shield and is everywhere clearly and sharply outlined (Fig. 36*b*). A day later this sharpness is lost, the bands of reddened skin are broader, the point of the unexposed triangle is lost, the triangle is much shortened, while the stem that attaches the triangle is lost or almost lost (Fig. 36*c*). Actually, when this photograph was taken, the skin originally protected by the triangle had assumed a full red colour at its margins and was pinker than the normal skin throughout its whole extent, with the exception of a small circular area of 2 mm. diameter near its base. The pinkness at this stage was seen to be of deeper and deeper tint as it was traced towards the apex of the triangle, thus helping to obliterate the latter. The bands of full redness surrounding the triangle now measured 2·8 to 3 mm. in breadth, and beyond their borders the less intense coloration diffused into the skin for a distance 1 to $1\frac{1}{2}$ mm. or farther. When the irradiation has been longer than 6 minutes, this added zone is broader, not uncommonly extending 4 or 5 millimetres, sometimes more, beyond the area of exposure.

The zone of extended redness will be further discussed ; here we may note that, arising from 3 to 6 minutes exposure it is transient, disappearing within 1 to 2 days of exposure ; that is to say, it lasts 24 or perhaps 48 hours. When it vanishes, it leaves the original local reddening sharply defined again and covering the precise area exposed. During the next few days, the local redness lessens, and in about 4 to 6 days from exposure is decidedly decreased ; in the same interval of time the skin assumes a browner tint, suggesting the beginning of pigmentation. The brown colour increases and is usually at its height in about 7 to 13 days, when the skin, which has become distinctly wrinkled on its surface, begins to scale away. Where scaling is complete, or large flakes have been lost, the skin beneath is found to be pink or red and, on expressing the blood from it, little more than a trace of pigmentation can be noticed. The pigment becomes more distinct as the days go by, the pink or red colour giving place to brown, which in its turn and over a period of many weeks or months gradually fades away.

In these relatively mild ultraviolet burns evidence of an increased blood-flow to the skin is usually lost in about 3 or 4 days after the exposure, a fact ascertained by repeated congestion tests. If, after these times, the skin of the arm is rendered cyanotic, the tint of the exposed area is not found to be pinker or redder than the surrounding skin, though it is darker in colour.

Reaction to longer exposures. The reaction to longer exposures (6 to 8 minutes or more) is in the first instance similar, though the initial local reddening is seen after a shorter period of latency. This local redness extends farther into the surrounding skin than after shorter exposures. The swelling and tenderness of the exposed area are more conspicuous, and its subsidence and the fading of all the colour reactions observed takes longer to complete.
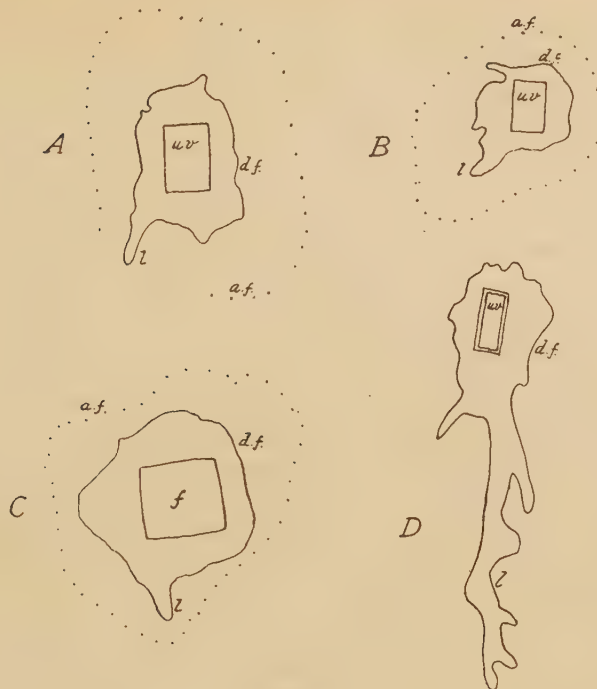
FIG. 34.

A. (× $\frac{2}{3}$.) Ultraviolet irradiation of 14 minutes; skin of forearm near elbow. Slight redness appeared 22 minutes after the end of exposure, the skin was red all over at 42 minutes. The diagram shows the condition 24 hours after exposure. The rectangle marked the area exposed and this was deep red. The continuous outline *d. f.* marked the diffusion flush with its lymphatic extension (*l*). The dotted outline (*a. f.*) marked a very faint arteriolar flare. The diffusion flush disappeared on the 3rd day. In this and the remaining figures the bottom of each diagram is proximal on the arm.

B. (× $\frac{2}{3}$.) Ultraviolet irradiation of 12 minutes; radial surface of lower forearm. Slight redness appeared at 45 minutes after the end of the exposure. In $4\frac{1}{2}$ hours a very slight diffusion flush appeared, which had increased to a breadth of 2 mm. by the 8th hour. The diagram illustrates the condition at the 23rd hour. The diffusion flush was wider and had a short lymphatic extension (*l*) up the arm. The surrounding skin, within the dotted outline, was slightly but definitely paler and pinker than the remaining skin of the arm.

C. (× $\frac{2}{3}$.) Skin of forearm frozen for 15 seconds near elbow at –15·1°C. Hard frost. $2\frac{1}{2}$ hours later the skin was still swollen and deep bright red in colour. Around it a faint bluish diffusion flush had formed. At 24 hours this flush was 5 mm. broad and presented a short extension. The diagram shows the condition at 48 hours. The square area frozen was bright red and now unswollen; it was surrounded by a broad bluish diffusion flush, having a short extension (*l*) up the arm. The surrounding skin (dotted outline) was quite distinctly pinker and paler than the remaining skin of the arm, and this contrast was enhanced by throwing 70 mm. pressure on to the veins. The diffusion flush receded to a breadth of 2 to 3 mm. in 3 days, and was invisible in 4 days, though paleness of the surrounding skin persisted for 6 days.

D. (× $\frac{2}{3}$.) Ultraviolet radiation of 20 minutes on lower part of forearm. Local redness began in 30 minutes, and was well defined in 80 minutes (see Fig. 37 *3*, page 125). At 7 hours the redness was full and had begun to extend beyond the marked area. At the 10th hour tenderness was present. At the 20th hour the exposed area was bright red and slightly swollen, the diffusion flush measuring 2 mm. in breadth, and the surrounding skin for a breadth of about 15 mm. was mottled by whiteness and pinkness. The diagram shows the condition at about the 26th hour, the diffusion flush had spread laterally and a long branching extension (*l*) ran up the forearm. The exposed area was now of paler colour and surrounded by a bright red rim. After 2 days the condition was much the same; the centre was yellow; the diffusion flush, however, was less distinct and had disappeared in 3 days. The exposed area lost its yellowness in 6 days, becoming red again. In 7 days the skin was wrinkled locally and peeling began in 11 days, leaving the base pink and slightly pigmented.

If the irradiation is prolonged to 15, 20 or 30 minutes, the swelling that is present on the next day may proceed to the formation of blisters.

It is usual after these long exposures to notice, 2 or 3 days after irradiation, that the deep redness of the skin actually irradiated has given place to paleness or even to a bright yellow colour, a change that is presumably due to the accumulation of white blood cells in the affected skin. This yellow area is surrounded by a vivid rim of redness, sharply defined on its inner margin where it joins the yellow centre, but diffusing gradually and for several or many millimetres into the surrounding and unexposed skin. The pale or yellow centre resumes its bright red colour in about 4 or 5 days after exposure and, subsequently, pigmentation, wrinkling and scaling away of the superficial layers of the corresponding skin area are seen.

The part of this reaction that merits emphasis, is the diffuse reddening of the surrounding unexposed skin. After long exposures, and whether blistering ultimately occurs or not, this diffuse reddening extends commonly 5 to 10 millimetres beyond the margin of the skin irradiated ; its border is notably irregular and not infrequently displays well defined outjutting processes. These outjutting processes are directed up the forearm, or less frequently across the arm, and have a length usually of a centimetre, a little more or less (*l* in Fig. 34, *A and B*). On occasions they can be traced farther. Amongst the longest we have seen are those outlined in Fig. 34*D* and in Fig. 35. The skin affected by the diffuse flush described is bluer in colour than is the central red area that it surrounds ; with its extensions it lasts, in the case of the longer exposures, for from 2 or 3 to as much as 6 days, being most distinct usually on the day immediately following irradiation.

There can be little doubt as to the cause of this flush. The skin in which it appears has not been exposed to ultraviolet light, yet its vessels dilate. They dilate first at the margin of the exposed area, and from this the process spreads into skin at a greater distance. This part of the reaction is attributed to a diffusion of vasodilator bodies from the area of damaged skin, and we term it the *diffusion flush*. The vasodilator substances, if present in sufficient quantity, spread up the lymphatic channels in a concentration adequate to produce dilatation of the minute vessels overlying these lymphatics for a shorter or longer distance. In one instance of a severe ultraviolet burn the vascular dilatation over the lymphatic channels was sufficiently clear to be photographed (Fig. 37, page 125) ; outlines of the same vessels, charted from time to time, are shown in Fig. 35 also, and full notes attached in the explanation. Six weeks after these observations were made a drop of 1 in 3,000 histamine was injected intradermally into the centre of the old ultraviolet burn area, then pigmented. Within a few minutes (Fig. 35 *D*) an oval wheal (*H*) formed locally and soon the two original lymphatic channels became marked out by deeply coloured and narrow bands of vasodilatation in the skin ; within 15 minutes of the injection, these bands of skin whealed. The outline Fig. 35 *D* represents the area of this whealed skin ; the outline of the accompanying arteriolar flare is omitted.

It is not uncommon to notice, at the time when the diffusion flush appears, and when it is at its height, namely, a day after the exposure, a further phenomenon in the surrounding skin. This is most noticeable outside
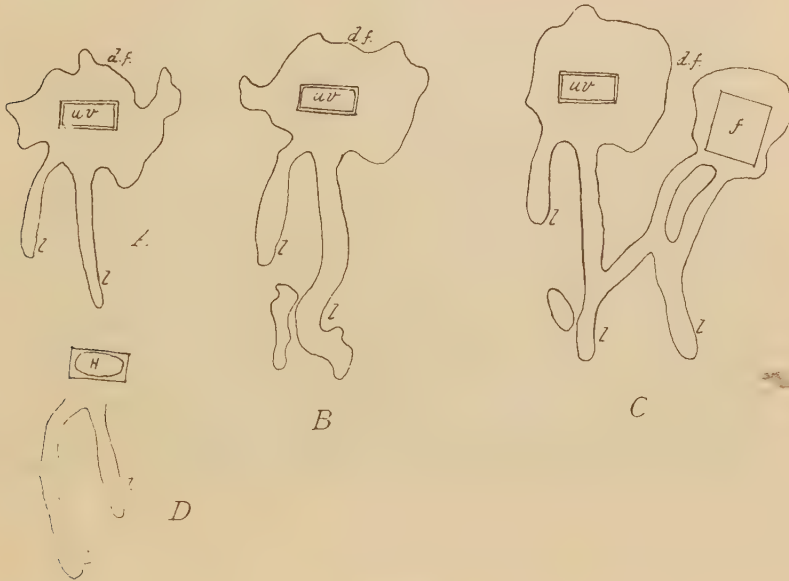
Fig. 35.

A. ($\times \frac{2}{3}$.) Ultraviolet irradiation of the forearm near elbow for 15 minutes. Reddening was developing within an hour and was full within 5 hours, when a slight extension was noticed. By the 7th hour the original ink marks were passed by $\frac{1}{2}$ mm.. By the 11th hour, the diffusion flush had a breadth of $\frac{1}{2}$ - $1\frac{1}{2}$ mm.. The condition at the 23rd hour is shown in the diagram A. The diffusion flush was wide and had two extensions (l, l) up the arm ; it was bluish in colour. At the 24th hour this area was irradiated again for 15 minutes. A photograph of the arm at the 27th hour is shown in Fig. 37, page 125 ; this reaction being displayed at *2*. At the 28th hour the lymphatic extensions were longer (*B*). The condition at the 48th hour is shown in *C*, to the left.

 The rectangle (f) to the right of *C* is an area frozen when this arm was first irradiated, and refrozen at 24 hours. At about 48 hours, when outlined, this frozen area was deep red and surrounded by a diffusion flush which extended up two lymphatic channels, one of which anastomosed with the corresponding extension from the irradiated area. Its condition at about 24 hours is shown in Fig. 37, page 125, at *4*, and the lymphatic extensions are here just visible.

 The irradiated area was bright yellow, with a surrounding narrow rim of bright red colour in 3 days, and blistered slightly 4 days after its first exposure. 8 days from exposure the diffusion flush was narrow and the lymphatic extension had disappeared.

D. Six weeks later the pigmented skin of the old ultraviolet burn was injected intradermally with a drop of 1 in 3,000 histamine, and the wheal outlined at *H* formed. Shortly two deep red bands appeared amidst the surrounding arteriolar flush and extended several centimetres up the arm. About 15 minutes after the injection these bands (*l*) presented distinct whealing throughout their courses, and were then outlined and charted.

the area of the diffusion flush itself and extends 0·5 to 1 centimetre or a little more beyond it (dotted outlines of Fig. 34 *A* and *B*). It consists of a very slight paling of this area of skin, associated with mottling of a somewhat pinker colour than that of the remaining skin of the arm. If, when the skin

Fig. 36. ($\times \frac{5}{6}$). Photograph of a forearm. (*a*) A black paper shield used in the following exposures. (*b*) Area of skin irradiated for 6 minutes, 4 hours before photographing. (*c*) Area of skin irradiated for 6 minutes, 28 hours before photographing. Notice that, while the area of ultra-violet reddening in *b* is everywhere almost sharply defined, even at the point of the protected triangle, in *c* the bright redness has invaded the protected skin, shortening the triangle, narrowing its stem and broadening the red bands on the exposed skin. This extension passed into a slighter and more diffuse flush which is also distinctly shown; the distinction between the first extension and this slighter flush was more conspicious in this instance than is usual. Actually, at the time of photographing, the whole interior triangle of skin was definitely pinker than the normal skin with the exception of a small area near the base of the triangle.

Fig. 37. Photograph of a forearm, showing a number of skin reactions.

1. A long narrow ultraviolet exposure of 3 minutes, made 24 hours before photographing. A wide diffusion flush is seen. 2. A rectangular ultraviolet exposure; the skin was exposed for 15 minutes, 3 hours and 27 hours, before photographing. A wide diffusion flush and lymphatic extensions are shown (*see* Fig. 35 *A*, *B* and *C*). 3. A rectangular ultraviolet exposure of 20 minutes, 1 hour and 20 minutes before photographing. The redness, which is well developed, has been outlined with dots of indian ink; the subsequent development of this reaction is shown in Fig. 34 *D*. 4. An area frozen a day before and a few hours before photographing. A faint diffusion flush is shown and indistinct lymphatic extensions from it (*see* Fig. 35 *C* right half).
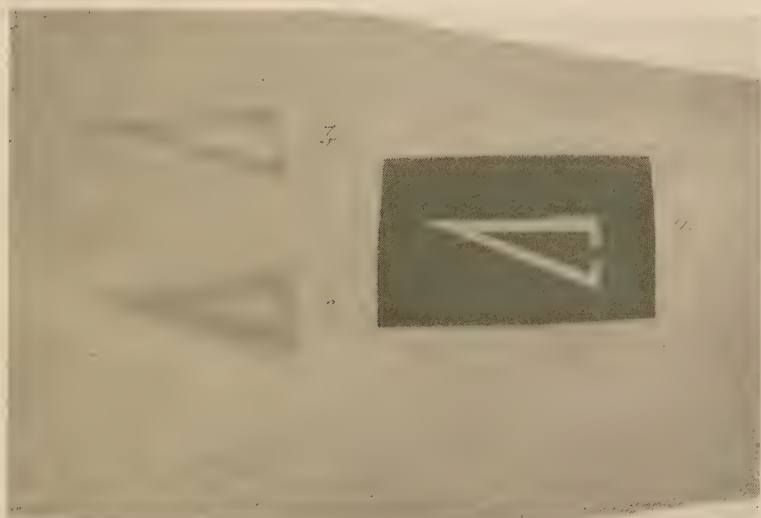
Fig. 36.

Fig. 37.

presents this area of pinkness and pallor, the venous pressure in the arm is increased, the area in question often stands out a little more clearly, being pinker than the surrounding skin, which is becoming cyanosed. The phenomenon is by no means invariable and is never conspicuous. Briefly, this area appears to be one in which an increased blood flow is just recognisable and in which capillary tone is relatively high.

The triple response to light and its cause. When the skin responds to such stimuli as are associated with a short period of latency, the reaction as we have seen is composite, being in two parts local and in one part reflex. This triple response, as it is usually seen, is due to the liberation of H-substance in the skin, a liberation which we have come to regard as fundamental to skin injuries as a whole. It remains to determine to what extent the response to ultraviolet light is comparable to this more immediate and familiar response and consistent with the proposition just stated.

Now it is clear that in the ultraviolet reaction we have to deal with an active dilatation of the minute blood vessels ; it is equally clear that the stimulus of light increases the permeability of these vessels locally, witness the usual slight whealing that follows short irradiation, and the blister that follows longer ones. Of the usual triple reaction the only part that fails to be *manifest* is the surrounding arteriolar flare. An indistinct change that may happen in the colour of the skin, for a considerable distance around an exposed area (Fig. 34 dotted outline), represents to our minds this flare. Its pinkness is consistent with its arteriolar origin, so is the increase of this pinkness by contrast when the skin of the arm is rendered cyanotic. It is true that this flush is indistinct and that paleness, rather than pinkness, often predominates ; but there is a good reason why this should be so.

In Chapter XIII it will be shown that when an arteriolar dilatation of reflex origin is long maintained, a balancing action occurs in the minute vessels of the corresponding territory ; these vessels contract and, in so doing, decrease the flare. In reactions occurring after a long latency, such as that to ultraviolet light, it is to be expected that the balancing action of the minute vessels will occur almost hand in hand with the development of the arteriolar flare, which as a consequence will be indistinct or will fail to appear. This explanation, as now put forward, is incomplete ; but it will be rendered complete at a later and more convenient stage.

In view of these considerations we may hesitate less in regarding the indistinct area of surrounding pallor and pinkness as in fact corresponding to the arteriolar flare of the triple response. Granted that this is so, then the ultraviolet reaction is built up of precisely the same components as is the more speedy response to other forms of injury ; this would in itself point to the light reaction being due to the presence of H-substance in the skin.

Conclusive support for the view that a vasodilator substance is released is found in evidence that the local reaction spreads beyond the limits of skin actually exposed to light. This spreading reaction consists usually of visible

vasodilatation only, but it may be accompanied on occasion by œdema also (*175*). It is reasonable to believe that the cellular structure of the skin is directly affected by the light only where this falls upon it ; this is the skin that at first becomes sharply defined by its redness and alone remains red in the stage of fading. This skin alone becomes yellow later, alone becomes pigmented ; and it is the only skin that eventually desquamates. While the reaction is at its height, however, the area of vasodilatation creeps from the injured into the uninjured skin, to form the diffusion flush. The manner of this spread, including extension along lymphatic channels, forms convincing evidence of the presence of vasodilator substance, formed locally and dispersed gradually through the tissue spaces and lymph ducts.

Now diffusion flushes are not peculiar to ultraviolet burns, they occur also as a sequel to firm strokes that have whealed the skin in the susceptible, and are best seen on the succeeding day. They also occur after the skin has been frozen and, in all their details of colour and form, correspond to those surrounding irradiated skin (Figs. 34 *C* and 35 *C*). In this same type of injury the central or injured area may also become widely surrounded by a slightly paler and pinker colour than that of the remainder of the arm (Fig. 34 *C*, dotted outline). These observations are important because they bring the reactions to ultraviolet light and to other forms of injury very closely into line ; they are also of interest from another point of view to be discussed presently.

The cell factor in reactions of short and long latency. The essential differences between the usual ultraviolet response and those previously considered is the long latency in the development of the former. When the skin is heavily stroked, submitted to burning heat, or frozen until converted to a solid mass of ice crystals, the damage caused to the cells of the skin must, from the nature of the physical agency employed, be almost instantaneous.

The discharge of the substance from the cell must be almost or quite simultaneous with the injury or, in the instance of frost, simultaneous with thawing, for the latent period of the vascular reaction that follows and for which the injury is responsible is measured by a few seconds, and is equalled by that to histamine introduced. Whether we regard the discharge as due to cell stimulation or to cell rupture, we shall regard the substance released as preformed* in the cell ; this idea, that in the acute reaction we may have to deal with normal metabolites, will receive further support in subsequent chapters (pages 149 and 186). So much for the cell factor when a reaction of short latency is initiated.

When we consider the reaction to ultraviolet light, the precise nature of the substance liberated may not be so clear at first. That it produces similar responses has been shown ; but we have yet to discuss whether or not, in the reactions of short and long latency, the substances are to be regarded as identical. The ultraviolet reaction proceeds slowly from first to last ; but, in comparing this with the more acute reactions, it has to be said that

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*Intending to convey that the substance is present as such, or in loose combination, in the cell.

in these the cells continue for many hours or several days to release the vasodilator substance, as evidenced by the diffusion flushes. Here, as also in the case of ultraviolet light, the suggestion is inevitable that products of cellular disintegration may be concerned. Desquamation, a sequel to almost all the forms of injury discussed, lends support to the supposition, since it may be read legitimately as the removal of the husks of killed cells. Thus, in the case of prompt injuries, we must for the moment remain receptive to the idea that the discharge of preformed metabolites is afterwards supplemented by the presence of the similarly acting products of dead or dying cells, though we may equally entertain the idea that the late discharge is but a continuation of the first. It does not seem possible to decide experimentally between the effects of cell death on the one hand and cell damage or cell stimulation on the other; for any injury that may be supposed to kill cells centrally may also be supposed to damage or stimulate others peripherally.

In the case of the ultraviolet light burn, if we suppose that normal metabolites are alone responsible, then long latency would be explained by supposing that increased activity, with its accompanying increased permeability of the cell walls, is produced initially in much smaller degree than in the case of the quicker responses. If we suppose that disintegration of the cells is in part responsible, then long latency would be explained by supposing, as we have every right to suppose, that the lethal effect of ultraviolet light is less abrupt. I say in part responsible for a definite reason now to be considered.

Just as there are instances in which a relatively mild stimulus, such as stroking or cooling, produces a full urticarial eruption of the skin, stimuli quite inadequate for this purpose when applied to the average skin, so there are cases on record in which there is an unusual susceptibility to the light stimulus. There are people whose skins react and yield bright erythema and full urticarial swelling, after a few minutes exposure either to strong or sometimes even to weak sunlight (Ward *259*, Ochs *200*, and Duke *71, 72*).* These instances are of much theoretical interest, not only because the type of response is changed, but because this change is associated with greatly diminished latency. The latent period appears to be from 2 to 5 minutes (*71, 259*), intervals of similar magnitude to those of the acute skin reactions described in previous chapters. Thus any remaining doubt as to the essential sameness of the chief mechanism underlying these acute responses and those to ultraviolet light disappears.

Thus we are left ultimately with the choice between two simple alternatives. Firstly, that both the acute and ultraviolet light injuries bring

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* The curious pathological responses known as summer prurigo and hydroa vacciniforme, the latter often though not always associated with hæmatoporphyria, have not as yet become relevant to the subject matter discussed. Reference may be made by those interested to Hausmann's very full summary of observations (*108*) and to Mayer-Betz's bold injection of hæmatoporphyrin into his own veins (*188*), followed as it was by acute susceptibility of his skin to sunlight.

vascular response through the sole agency of preformed or normal meta-
bolites ; or secondly, that this is in each case the main agency, but that it
becomes supplemented by the action of disintegration products. In either
case we assume that mechanical injury or frost promptly liberates a substance
in large amount and concentration, and that subsequently it is liberated in
smaller amount ; and that, in the usual reaction to ultraviolet light, the
liberation is gradual and continuous and the concentration less from the
first.

The essential difference between the ultraviolet light reaction and the
remainder, therefore, is really to be found in the manner in which the
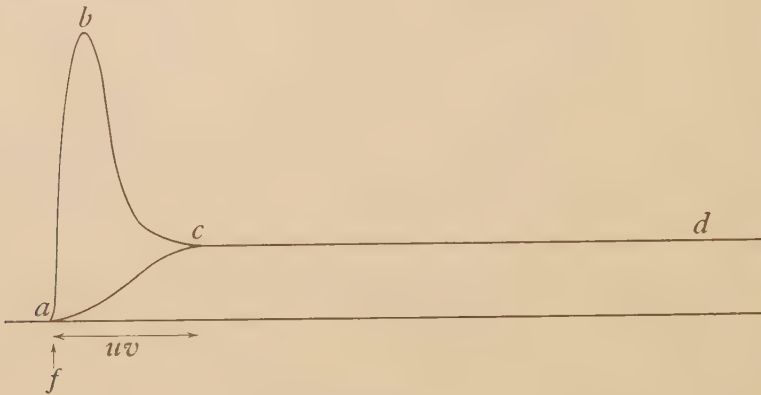
Fig. 38.

liberation of the substance is initiated. These releases are summed up
diagrammatically in Fig. 38. The curve *abd* represents that occurring in the
case of acute reactions to such a stimulus as freezing (*f*), while the curve *acd*
represents the release of such a reaction of long latency as ultraviolet light,
acting over the period marked by the arrow *uv*.

The influence of latency upon the response.—We return to the question
of why the surrounding arteriolar flare is so little in evidence. One reason
has been assigned for this already, namely, a balancing contraction of the
minute vessels. This accounts for the occasional paleness of the suspected
zone or for a mottling of pink and pale areas similarly situated. Nevertheless,
we may not postulate a full arteriolar dilatation, concealed by a balancing
action of the corresponding minute vessels ; for, in the area actually injured,
where the minute vessels are widely dilated and where there can be no
question of their exerting a balancing effect, the rise of temperature is far
less than it would be if the arterioles supplying it were fully open. Thus,
the condition of the injured area itself precludes us from supposing that the
arteriolar dilatation following an ultraviolet burn is equal in its degree to
that following such injuries as burning or freezing ; but the local reaction

of the minute vessels becomes full in the same circumstances ; thus, there is an actual disparity between these two parts of the whole reaction in the case of the ultraviolet burn.

The reason for this disparity is to be found in the slow development of the reaction, for this implies that the released substance responsible for it appears in the tissue spaces in weak concentration. Experience shows that to produce a widespread arteriolar flare it is in general necessary to employ a stronger stimulus than is required to produce a local dilatation of the minute vessels. This is emphatically the case with mechanical stimuli, as has been stated in Chapters III and V. It is possible to produce even vivid local reactions on some skins by stroking them, while the flare remains in little evidence. The same statements apply to other forms of stimulus when these are nicely regulated. These facts are interpreted in the sense that the concentration of H-substance requisite to stimulate the nerve endings, and thus to produce the flare, is greater than is that required to act on the vessels locally.

There is a further characteristic of the local vasodilatation ; in general it develops more slowly to its maximal point, and this point is much longer held, than is the case with the flare, the latter being timed by following the visible redness or the skin temperature. Even in the case of stroking this is often so, provided the strokes are heavy ; the red line may even fade away, a little or much, to return with renewed intensity later, and it may then last for hours ; meanwhile the surrounding flare soon fades away and is not subsequently seen. In the case of the freeze or the burn it is the rule for the deepest local reddening of the skin to be seen long after the flare has subsided, and for this vivid redness to persist long after the temperature of the skin at the point injured has fallen to normal.

These observations upon reactions starting acutely are explained as follows :—the strong stimulus instantly releases the H-substance in a concentration adequate to excite the nerve endings ; this concentration soon diminishes in the tissue spaces and to a point at which it becomes inadequate to the same end (Fig. 38) ; but H-substance continues to be discharged from the affected cells in smaller quantities than originally and continues to act on the endothelial vessels. Thus, the latter are maintained in a dilated condition, or are even increased in width by cumulative action. A weaker stimulus will release the substance in small quantities and the concentration may never rise to a point adequate to rouse the nerve endings, though it may be sufficient to cause a response in the endothelial vessels, at once in the case of a mechanical stimulus, or after delay and by cumulative action in the case of the stimulus of ultraviolet light.

Whether the hypothesis, to remain acceptable, takes this form or assumes a modified form, matters little from the standpoint of my main theory. It is clear that as long as we can reasonably explain, on the basis of the tissue factor, the differences in the triple response to quickly acting stimuli on the one hand and to slowly acting stimuli on the other, these

differences cannot be held to point to the intervention of mechanisms fundamentally different in the two instances.

So far as the amount of œdema is concerned, this will naturally vary in the case of an ultraviolet burn as it does in the response to stroking. In the latter instance it is the rule (see page 71) to find that œdema and arteriolar dilatation, as represented by the flare, develop more or less proportionately. A rapid transudation is not possible in the case of the ultraviolet reaction ; the blood supply to the tissue concerned is insufficient. With slow transudation, and absorption playing a more evenly balanced rôle, the rate of accumulation will be relatively slow ; and there will be opportunity for a balance to be struck at a comparatively early stage of accumulation. Variation in this respect there will be, owing to variations in the two sides of the balance. Another factor operating sooner or later will be refractoriness ; when this comes, permeability will decrease and transudation will tend to come to an end.

X ray and radium emanations.

The example of ultraviolet light has for us the importance of demonstrating how the usual or type reaction, which is acute, may be modified by the form of stimulus employed. If it is admitted, and I think it must be, that the vascular reaction of the skin to ultraviolet light is of the same essential nature as is that to forms of stimulus previously considered, then the reactions to X ray and to radium emanations can clearly be brought into the same category. These both yield local reddening, and sometimes swelling of the skin, indistinguishable in type from that of ultraviolet light. In both instances the reddening is associated with a sharply defined area of minute vessel dilatation, capillaries, venules and terminal arterioles participating. In these the latency is still longer, being usually from 2 to 5 or more days in the case of X rays, and from 2 to 3 or more weeks in the case of radium. Once the ultraviolet reaction is interpreted, these examples give rise to no difficulty.

In this connection it is to be stated that in both these examples a long lasting effect is known from independent sources to be exerted on the nutrition of the cells of the skin ; I refer to the very delayed granulomatous and ulcerous manifestations, which skin exposed to these influences is apt to display. The question left for solution does not concern the mechanism through which the vessels respond, but concerns the mysterious way in which the cells are damaged.*

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* In Chapter xviii further evidence is brought forward linking the effects of ultraviolet light, X ray and radium emanations with those of the more quickly acting stimuli, for in all these instances the vessels are found to be left in a common state of refractoriness to histamine and irresponsiveness to vasoconstrictor substances.

Reactions to bacterial poisons.

Similarly we shall have almost certainly to include inflammatory reactions to bacterial poisons in the same fundamental class, and to acknowledge that these also result, in so far as the vessels are involved, in essentially the same manner.   Reactions of the cutaneous vessels to these are illustrated by the tests of Dick (*64*) or of Schick (*190*).

A small quantity of streptococcic or of diptheritic toxin is injected intracutaneously and, within a day in the first instance or 2 to 3 days in the second, the reaction is at its height in susceptible people. The colour of the skin becomes of an intense pink, not scarlet, and it becomes duller as it fades ; it is accompanied by, and is coextensive with, a swelling of the skin. Signs of a surrounding arteriolar flare are indistinct, more usually absent.   The local reddening stands out brightly on skin rendered blue by a congestion test. The temperature is raised locally, though rarely by more than 0·5°C, and there may be tenderness. If the circulation to the limb is stopped and the blood is massaged out of the vessels, it returns immediately and the original contour of highly coloured skin is at once resumed. It is due, therefore, to an active dilatation of the minute blood vessels.

The reaction, in so far as it has been described, is in every way comparable to a rather severe ultraviolet light burn. It differs from the latter in the following minor respects. The reaction spreads as an intense reaction beyond the area of skin originally involved, and œdema is more in evidence. This is especially so in the instance of the Dick reaction, which is more severe. This diffusion, like that seen in the case of relatively severe ultraviolet burns, destroys the crispness of the margins of the reaction. It is to be remembered that in these instances, a quantity of poison is introduced into the skin and this may, and in all probability does, remain in the skin for a considerable while, itself diffusing into surrounding skin.

It is not within the scope of this book to discuss the meaning of the latency in these inflammatory reactions, other than to point out that such latency is invariable in the reaction of the tissues to bacterial poisoning, whether these are introduced locally or into the general circulation, and that the problem here involved concerns, not vascular response, but the mechanism by which the cells receive their injury.

It is relevant to point out, however, that assuming the view to be correct that in local injury by bacterial poisons a release of H-substance occurs, then the general intoxication that follows bacterial invasions of the body must often include effects produced by this substance entering the general circulation. Many of the symptoms that are common to invasions by bacteria of distinct kinds would thus be explained, and the resemblance of these symptoms to those of secondary wound shock (see page 110) would become more clearly understood.

CHAPTER IX.

Reactions to certain chemical substances.

Our knowledge of the reactions of the skin to chemical substances in which considerable latency is displayed, still leaves much to be desired. The latency in the reaction to certain substances, such as iodine and copper sulphate, that are fairly soluble in water, seems to be a little prolonged when compared with that of other and more soluble poisons previously discussed (*see* Chapter IV) ; but there are substances very slightly soluble in water, of which dichloroethyl sulphide may be taken as a type, to which the response comes after conspicuous latency.

Dichloroethyl sulphide. This sulphide is a substance that, under the name of mustard gas, has taken a prominent place in gas warfare, and for general accounts of its massive action I refer to the book by Warthin and Weller (*260, see also* Soltau *230*). It is an oily fluid that is very sparingly soluble in water, but readily soluble in acetone and, what is here particularly significant, in fats. This attraction to fatty substances is so great that a man exposed to a very dilute mustard gas vapour, for example one who walks through gassed territory, may be severely poisoned, the poisoning consisting of severe irritation of the skin and mucous membranes. The developed reaction is a violent one, consisting in the case of the skin of brilliant erythema, whealing and blistering, and in certain cases, ulceration and loss of tissue.

From these profound effects of very dilute vapour on the skin, and from the no less profound but far more serious action on the respiratory tract, the gas has come to be regarded, erroneously so I think, as a very powerful irritant. The danger of the substance lies, not in its strength, but in its ability to concentrate in the skin, and in its clinging properties.

If a drop of concentrated mustard gas (0·3 or 0·5 c.mm.) is placed on the surface of the skin, the events that follow are briefly as follows.[*] Within 1 to 2 hours, reddening begins in the skin ; this redness deepens during the next few hours, is sharply defined, and accurately marks out the area moistened by the poison. Within as a rule 6 to 12 hours the skin is raised, and within 12 to 48 hours, though sometimes earlier, blistering is observed. It is unusual to see a surrounding flare, though this is unmistakable in some instances. In relatively mild reactions the blister dries, or fails to develop, but some swelling and redness persist, the latter for many days or weeks. Eventually and gradually the skin becomes deeply pigmented and this pigmentation lasts for many months. In more severe burns the superficial skin is killed and comes away in the form of a dry scale or scab, which separates very slowly, and the lesion leaves when healed a silvery scar in the skin.

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[*] The events described are those which I have myself witnessed and agree with the previous accounts by Warthin (*260*) and Soltau (*230*).

We are concerned with the vascular parts of this reaction. The local initial reddening is seen microscopically to involve all the minute vessels of the skin, and tests, similar to those described in the case of ultraviolet light, similarly show that this dilatation is an active and not a passive effect. The initial reddening is in fact indistinguishable, by any test I have been able to devise, from that produced by ultraviolet light. We have to deal with a reaction consisting of the usual components. A local and active dilatation of the minute vessels, an increase in the permeability of the vessel walls locally, and, thirdly, a surrounding flare, which, as in the case of ultraviolet light and for similar reasons, is often indistinct or fails to be manifested.

This is the familiar triple response, modified by its slow development. The local reaction, namely, reddening and œdema, is independent of a nervous mechanism, central or local* ; the arteriolar flare, and this alone, is due to a local nervous reflex, failing to occur on skin to which the nerves have degenerated (*167*). Thus, the response to mustard gas falls very precisely into line with other slow reactions of the skin to injury.

It would certainly be useful for practical purposes to know the minimal effective dilution in which substances applied to the surface of the skin act ; but this method does not tell us even approximately how potent the substances are as protoplasmic poisons. For the tests take no account of the relative powers of the substances to penetrate, nor of changes in strength, in the directions of dilution or concentration, that may take place after they are applied. There are many powerful irritants readily soluble in water, which are inert when placed in high concentration on the skin ; histamine phosphate is one such ; and its failure to stimulate is due to failure to penetrate. It will be evident in general that water soluble substances in penetrating will tend to be diluted in the process to an extent that oil soluble substances will not, and that the latter, when brought to the skin in the form of dilute vapour, or dissolved in highly volatile acetone, will become concentrated in the skin. A comparison of effective concentrations is more reasonable when the substances compared are placed in direct contact with living cells.

If concentrated mustard gas is carried into the skin, by pricking the skin with a glass capillary tube, the bore of which has a diameter of 0·1 mm., and which is filled with the oil,† any reaction that occurs then or later is so slight as to be indistinguishable from that given by a capillary tube filled with normal saline ; a similar experiment carried out with 1 in 30,000 histamine, or with 1 in 200 morphine hydrochloride, or with many other substances in high dilution, yields an unmistakable and almost immediate response. In fact there are but few substances, so administered, that are capable of

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* This conclusion is to be taken emphatically, despite statements which have been made in the contrary sense (*65*). The conflict of evidence appears to have arisen in the same way as it has arisen in the case of ultraviolet light, fully discussed on page 118. Nerve section, and especially local anæsthesia, may modify the local reaction but does not influence it fundamentally.

† A needle should not be driven through a drop of the oil placed on the surface, for the surface drop will itself cause a reaction eventually.

producing an acute and manifest reaction, which are not freely or fairly freely soluble in water ; and this is natural because interchange with the contents of living cells depends upon such solubility.

Further, if we judge the strength of irritant substances by the dose required to produce a reaction, then again mustard gas is found to be an extremely weak irritant. A reaction produced in several hours by 0·3 c.mm. of mustard gas is exceeded within a few minutes by 0·000001 of a milligramme* of histamine.

In comparing the strength of irritants there is this other important consideration, namely, the length of time that they remain in contact with the cells they irritate. Acids and alkalis being freely soluble in water rapidly become diluted, are thus rendered inert, and they are soon removed ; mustard gas and other irritants that are soluble in fat but little soluble in water remain in place and their irritant action may be presumed to continue. From every suitable standpoint of measure, therefore, mustard gas comes to be regarded as a relatively innocuous substance. Its apparent strength comes from its power to penetrate the skin in a relatively undiluted state and, penetrating, to remain there.

Cantharadin. An irritant substance giving effects very similar to those of mustard gas is crystalline cantharadin, with which I have compared it ; but cantharadin is the more potent. If a solution of this substance in acetone † is punctured into the skin by means of a capillary tube, the immediate reaction usually takes the form of a small wheal surrounded by a flare ; this wheal very gradually becomes a blister within the space of 3 to 5 hours , mustard gas similarly administered is, as we have seen, without effect. If equal drops (0·3 c.mm.) of 2·5 per cent. mustard gas and 2·5 per cent. cantharadin, both in acetone, are placed on the unbroken skin, either one or other may produce a simple reddening over the area of contact, either may fail to do so, and this is the more frequent with cantharadin. Reddening, if it appears at all, comes in an hour or two in both instances, but no surrounding flare is visible in either case. If the skin is first scratched with the point of a needle and the drops are similarly applied for comparison, both usually cause local reddening within an hour or two, but blistering is rarely seen except in the case of cantharadin, and it is then confined to the line scratched. Otherwise the two reactions occur in much the same time intervals, and are almost indistinguishable.

I conclude that, in so far as these two substances may be said to differ, cantharadin has the slightly greater irritant power ; it is just sufficiently potent to produce an immediate effect in the form of a wheal ; but placed on the unbroken skin, it does not penetrate so readily as does mustard gas.

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* Say 1/30 c.mm. of a 1 in 30,000 solution.

† The strength of the solution is not of consequence, because the acetone evaporates at the end of the tube and little crystals quickly form there ; the dose must be regarded, therefore, as a minute particle of cantharadin crystal.

Chloroform. This is another weak irritant and illustrates the effects of low solubility in water and relatively quick penetration.* If a capillary tube containing pure chloroform is driven into the skin, a reaction follows in a few minutes. This is of the usual type ; a wheal forms, but there is no blistering. The irritant may be said to be a weak one because, to produce whealing, the substance must be used in high concentration. If a glass tube of pure chloroform is inverted on the skin and gently held in place, a little smarting is felt in about 2 minutes. This increases in severity and soon a flush is seen to extend through the surrounding skin. If the tube is removed at about 5 minutes, local reddening is seen and there may be slight whealing. If the tube is removed at the end of 10 to 15 minutes the wheal is usually seen or soon develops, and, a considerable while later (1 to 2 hours) a blister develops locally.

Thus, concentrated chloroform introduced directly to the living cells and remaining with them undiluted, for but a short while, yields the usual acute reaction ; placed against the unbroken skin it certainly begins to penetrate to the living cells within 2 minutes ; retained against the skin, it reaches the cells in sufficient concentration to produce whealing in about 5 minutes. Only when its action is prolonged to double or treble this time do blisters form, and they then form after a further and prolonged delay.

We may be content for the moment to regard this action as one of continued irritation, whereby the cells concerned are brought into a state in which they continue slowly to discharge H-substance into the tissue spaces ; the condition of the cells would then be comparable to that supposedly occurring in the instance of ultraviolet light, though, in this last instance, the condition is brought about by a stimulus that is not continued while the reaction develops.

The action of all the slowly acting substances named—and many others having similar physical properties might be added to the list—have a peculiarity in common with ultraviolet light. Once applied as stimuli the reaction has a very notable tendency to end in blistering. This may or may not indicate the intervention of a new factor. Though the first view has been expressed (Heubner 115), the second is, I believe, more probably the true one, and for the following reasons. Nearly every form of stimulus that produces whealing, when applied to the skin will lead to blistering if rendered more intense or if continued. The burn and the freeze may be named as two such, so may acids and alkalis. Although I have failed to obtain blistering in susceptible skin by stroking, repeated 10 or 20 times, yet it does occur with long continued friction. In response to artificial stimuli blisters always develop much less suddenly than do wheals ; this is so in the case of the burn, freeze and ultraviolet irradiation, and with the chemical substances that have been considered in this chapter. There is a very distinct relation between slowness

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* Oil of mustard (allyl isothiocyanate) might have been used as an alternative illustration in almost all particulars.

of action and blistering. I have also failed so far to obtain blistering with histamine itself, though the strength of this substance has been raised in solution to 1 in 5. This, the most significant failure, may be attributed to sudden introduction. It is very possible that, if histamine could be passed very gradually into the skin, it would cause blistering.

For the reasons given it seems to me improbable that between the wheal and the blister there is any fundamental distinction in so far vascular mechanism is concerned ; in actual fact the blister when it appears, almost always follows upon the wheal ; and if this sequence is not invariable, the blister may be said, nevertheless, to replace the wheal, and thus to represent, as otherwise would the wheal, the third factor in the triple response, namely, increased permeability of the vessel walls.

It is quite conceivable that when this difference in reaction, which I regard as a minor one, comes more clearly to be understood, its cause will be found to depend in part upon the manner in which the vessels become refractory and their permeability declines. In the case of the wheal the outpouring of fluid is rapid, and here the onset of refractoriness and the accompanying decline of increased permeability seem to be abrupt ; whereas, in the case of the blister, the fluid transudes much more slowly and continuously, and it would seem that refractoriness sets in more gradually and may on that account be less effective in checking transudation before it reaches the point at which the epidermal layers of the skin are forced asunder.

The present chapter has dealt with a variety of slowly acting stimuli, and we have seen that the reaction of the skin to these is fundamentally of the same kind as to quickly acting stimuli. Longer latency signifies a difference in the manner in which the stimulus acts upon the cell, it does not necessarily or even probably imply a difference in the nature of the response. But the long latency modifies the visible response. Because, after considering reactions of long latency, I am unable to decide whether injuries to the skin bring their vascular responses solely through the action of a common form of normal metabolite, or whether these are eventually supplemented by disintegration products, I have allowed the definition of H-substance on page 105 to embrace more than one substance.

It is concluded that all the stimuli considered, those acting promptly and those more slowly, awaken vascular response through the agency of the H-substance as this has been defined.

CHAPTER X.

SOME EFFECTS OF TEMPERATURE.

IN a healthy person, resting or moving quietly about in rooms at 18 to 20°C, those portions of the skin that are clad show usual temperatures of 30° to 34°C. I define these as normal skin temperatures. If the forearm is immersed in water above 34° or below 30°C, we are usually correct in saying that the skin has been warmed or cooled, respectively.

In the present chapter I propose to consider the known effects upon the skin of temperatures that fall short of obviously injuring the skin ; the effects of burning heat, of freezing, and also the occasional effects of super-cooling having been discussed fully in previous chapters. The effects of moderate temperatures are most conveniently studied by immersing the skin in water. Naturally, the skin warms or cools much more rapidly and thoroughly when exposed to water than when exposed to air of the same temperature, just as it responds more quickly to a metallic contact than to immersion. Exposure to air of different temperatures is unsatisfactory for most experimental purposes, because the response is relatively slow and is influenced greatly by atmospheric humidity and air currents. Exposure to metallic surfaces is usually unsatisfactory because contact is impossible without exerting undue pressure on the skin.

It may be well first of all to note the influence of immersion upon the temperature of the skin. The temperature of the skin surface changes promptly and approaches closely that of the water in which it is immersed ; it does not come precisely to the water temperature, for the skin cools or warms the immediately surrounding water. When the arm is held still in hot or cold water, its surface temperature may be several degrees below or above that of the bath ; equality of the two temperatures is approached more nearly if the water is constantly stirred. Now it is usually desirable to keep the water still ; the bath temperatures subsequently referred to are therefore those of unstirred water, unless it is stated to the contrary. A more important matter is the change of subcutaneous temperature, ascertained by means of a thermo-electric junction thrust in so that its point lies immediately beneath the true skin. Such investigations are sufficiently illustrated by means of the accompanying chart (Fig. 39), compiled from observations in which the skin of the arm has been explored in this way. Before each observation begins the arm is warm, its surface temperature being about 31°, and the subcutaneous temperature

about 34°C. The arm, into which the thermo-electric needle has been intro-
duced previously, is plunged into baths at 41°, 20°, or 11°C. The subcu-
taneous temperature rises or falls steeply, the greater part of this change
being accomplished within a minute of immersion ; subsequently the rise
or fall is slower and the line of temperature eventually becomes horizontal.
The reading represented by the horizontal line diverges from that of the bath
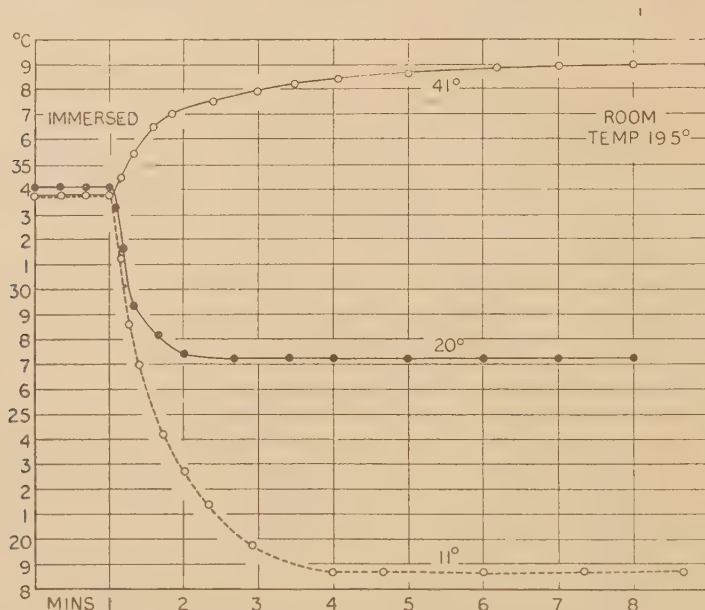
Fig. 39. To illustrate the effect upon subcutaneous temperature of plunging the warm arm into
water at temperatures of 41°, 20° and 11°C, respectively.

water by varying quantities, namely, from 0 to 7 or more degrees. The
temperature of the skin as a whole is to be regarded as lying between bath
and subcutaneous temperature. The greater the original difference of tem-
perature, the longer does it take for subcutaneous temperature .to become
stable and the greater is the ultimate divergence ; stability is reached more
quickly in the cold than in the hot bath. While the skin is cooled or heated
from outside, it is at the same time heated or cooled by the circulating blood
from within ; the rate of circulation in the skin consequently influences the
rate of temperature change in the skin, and the level of temperature actually
reached. The change is more rapid and is more profound if prior to immersion
the circulation to the limb is arrested. Generally speaking it is sufficient to
convey an idea of the degree of heating or cooling of the skin by referring to
the temperature of the bath and length of immersion ; there are occasions
when the expression needs to be more precise.

    These preliminary remarks, however, are mainly intended to make it
clear that bath temperature is not equivalent to skin temperature, and to

convey an idea of the magnitude of possible errors arising out of a contrary assumption.

Red response to heat.

If the arm of a normal person is immersed in water as hot as can be borne, the bath temperature is usually found to be between 45° and 48°C (*160*). The highest temperatures of this group are just within the range of those at which manifest but early signs of injury to the skin are detected, when, as previously described, the subcutaneous temperature rises to about 40°C (*171*). It is slightly lower temperatures that we shall now consider.

Reddening just sufficient to produce a definite line of demarcation between heated and unheated skin is found after a 5 minute immersion in water at 38° to 40°C or thereabout, the skin surface being at about 36° to 38°C (*171*). Temperatures of 43° to 45° produce a familiar and bright local reddening of the skin. The origin of the corresponding vasodilatation is complex. So far as the bright reddening is concerned, it appears to be maximal before the end of the third minute of immersion is reached, a time period suitable for many observations. It is improbable, however, that heating of this duration usually suffices to bring the vascular reaction in the limb as a whole to its maximal point, since the volume of the limb can be shown to continue its increase for periods extending to ten or fifteen minutes or somewhat longer (*165*).

Bruns and König (*35*) examined the skin of the hand reddened by a temperature of 42°C and noted increased pulsation of the digital arteries, widening of the subcutaneous veins, and increased flow in the minute vessels microscopically. Widening of a superficial artery by heat is best displayed by applying hot (45°C) and cold water (10° to 15°C) alternately to the temple, or to the scalp well away from the temple ; after the heating, a superficial temporal artery, hitherto invisible, often becomes conspicuous and, as it expands, more tortuous (*160*). Conspicuousness and tortuosity of this vessel is common in healthy people, young and old ; it is due to low tone of the vessel walls and may be reduced or caused to disappear by applying cold. Thus, heat applied to the skin not only dilates the vessels of the skin itself, but also the parent trunks. This last action must clearly be reflex, since little or none of the heat actually reaches the vessel concerned.

The reflex effect of heat is also shown in the case of the veins. It is well known that, if the hand is immersed in hot water, the veins on its dorsum increase in size and soon become turgid. The fact does not warrant us, however, in concluding that the walls of the veins have lost tone ; such increase in size might be the simple result of enhanced pressure within them. To test the matter the veins should be examined while congested to a constant and suitable pressure point, *i.e.*, 30 to 50 mm. Hg. A congesting pressure of this amount is thrown upon the veins and the hand is maintained in water at 10° to 15°C for 3 minutes, when the size of the veins is measured or the hand

photographed. The pressure is then released and, after an interval for the recovery of natural skin temperature and colour, the observation is repeated, congestion being reimposed and maintained for 3 minutes, while the hand is immersed in water at 45°C. The veins are now found to be increased notably in size, a change which, in the circumstances of the experiment, can be due only to loss of tone in their walls ; it is to be observed too that this increase in size is not confined to the veins actually immersed, but extends to the veins of the forearm. Donegan (*67*), working upon dogs, observed that venous tone is relaxed by heat and increased by cold, but only when the nerves to the limb remain intact.

These reflex changes in large subcutaneous vessels are but part of a central reflex extending to vessels of smaller size ; as Stewart (*235*) has demonstrated, the heat loss from the right hand* is much decreased by soaking the left hand in cold water, and I have seen its volume decrease sharply to the same stimulus, clear indications that the vessels of the right hand have become constricted ; the reverse effects are seen on warming the left hand. The increased flow and volume must be due mainly to expansion of the arterioles of the limb as a whole, and we may assume that those of the skin are likewise involved.† There are no observations demonstrating that the central reflex effect of heat is carried beyond the strong arterioles to arterioles of smaller calibre, though such an effect is possible.

So much for the minor effects on the main vessels ; we come now to the more important local effects.

The chief visible change in the hand soaked in water at 43° to 45°C is its reddening. Most of this reddening is a direct action in the sense that it is independent of central nervous system and of local reflexes. If the skin is anæsthetised by the subcutaneous injection of 2 per cent. novocaine, or better still if cases of old standing sensory nerve injury are examined, and the skin is immersed in water at the stated temperature, the sensitive and insensitive skin cannot be distinguished by the depth of redness exhibited (*160*). Microscopic examination of the skin flushed by such heat demonstrates that all the minute vessels are dilated (*43*).

This locally produced dilatation is, at least in large part, active. If in a cool room the circulation to an arm is brought to a standstill, and after a minute the hand and lower part of the forearm are immersed and kept still in water at 40° to 43°C‡ for 3 minutes, the skin of the arm becomes cyanosed,

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* Goldschmidt and Light (*97*) find that this, the measured arm, responds best when it is surrounded by water at temperatures of from 25° to 34°C.

† Ricker and Regendanz (*218*) saw the arteries at the base of the rabbit's ear dilate when the tip of the ear was dipped in water at 52°C. The observation is not necessarily relevant, since the temperature exceeds that which is tolerated by the skin and certainly includes the effects of gross tissue damage.
Further observations upon the effects of temperature on local circulation in animals will be found in Natus's paper (*198*), which deals with the rabbit's pancreas, and in Florey's paper (*85*), which deals with the dog's brain.

‡ The somewhat lower temperature must be used, because, when the circulation is obstructed, the skin feels the heat more fully.

but the part of it that is heated assumes the deeper colour, there being often a sharp line of demarcation between heated and unheated areas (*160*). Thus, the vessels that are responsible for skin colour are directly involved.

In the congestion test the arm becomes cyanotic. If now, or from the start, the arm is half plunged in water at 43° to 45°C, the colour of the immersed skin becomes red and the line between heated and unheated skin is quite sharply defined by the colour reaction. This demonstrates that locally the heat quickens the blood flow to the skin (*160*); the vessels responsible belong to the smallest orders, since reddening cannot be observed to spread above the actual water line, and since it can be produced by very local heating; however small the area of skin immersed, this, and this alone, is appreciably reddened. The local nervous reflex that brings a surrounding flare is not detected at these water temperatures. Anæsthetic skin is similarly and equally affected (*160*).

To sum up, it may be said that the effects of heat that is easily tolerated are several. They are brought about in part through the central nervous system, the larger arteries and veins and their branches losing tone reflexly. In so far as reddening of the skin is concerned, this is due chiefly if not entirely to an action that is independent of the nervous system and that is exerted almost if not quite exclusively upon the minute vessels themselves.

Red response to cold.

It is a familiar fact that when snow is handled or the hands are long immersed in very cold water, the skin becomes of a bright red colour. If a normal and warm hand is immersed in water at from 0° to 10°C and the other at 45°, the final colours assumed by the two hands are practically indistinguishable; reddening is in both cases bright and intense (*171*). The range of temperatures over which cold reddens the skin varies slightly in normal subjects. A 10 minute immersion at 15°C reddens the hands of some; immersion for this period at 10°C reddens the skin of most healthy people (*97, 171*). Immersion at 5° or at 0°C always reddens the normal skin (*43,171*). To test lower temperatures, cooled alcohol (50 per cent. strength) or a draught of very cold air has been used, and it has been shown that the skin displays the red reaction in from 3 to 10 minutes at all temperatures tested down to -25°C (*171*). A slight initial cyanosis, and perhaps transient pallor, may be seen at any of these temperatures, but it is redness that ultimately prevails.

In the skin reddened by cold water and examined microscopically the circulation is seen to be extremely slow, but the minute vessels are naturally found to be dilated (*35, 43*). This is primary and not the passive result of arteriolar dilatation, since it also occurs after arresting the circulation to the limb.

The deep colour of the skin reaches sharply to the water line and it is therefore clear that the main effect is confined to the minute vessels of the skin. Goldschmidt and Light (*97*) express the view that it arises in part

from venous constriction of reflex origin. It is true that the subcutaneous veins are seen to become smaller, but that their constriction materially adds to the congestion of the minute vessels is incompatible with the precise demarcation of the redness ; an appreciable effect from reflex constriction is opposed by the fact that the colour reactions to cold here described are unaltered when the nerves to the tested skin have degenerated (*28, 167*). The *slow stream* is usually and probably correctly ascribed to contraction of the (strong) arterioles of the skin.

The *red colour* is due to gaseous interchange between the blood and tissues having practically ceased ; although it is so slow in moving forward, the blood traverses capillaries and venules in an arterial state, giving up little or none of its oxygen. It is evident from Brown and Hill's dissociation curves (*31*) that blood in the minute vessels can give up little or none of its oxygen from 10°C downwards ; at similar temperatures the metabolic power of the tissues is also very much reduced. These changes with low temperature sufficiently account for oxygen being retained in the blood as it passes through the capillaries (*171*). A somewhat similar explanation is given by Goldschmidt and Light (*97*).
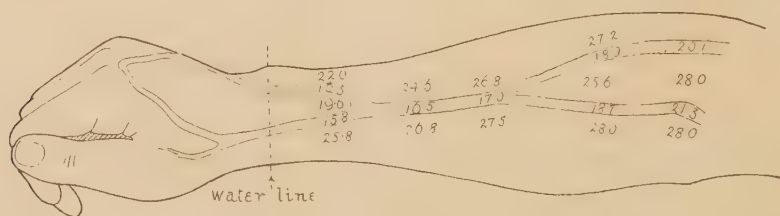
Fig. 40. (× ¼) A diagram showing the effect of immersing the hand in ice cold water upon the temperature of the unimmersed skin overlying the superficial veins of the arm.

The circulation in the skin is not normally brought to rest by cold however intense ; the slow stream continues and will continue even if the vessels are simultaneously congested by applying pressure to the veins. A hand rendered cyanotic by this means becomes red eventually in all its parts when immersed in very cold fluids, even though the obstruction to venous flow is maintained (*171*).

If congestion is caused and maintained in the arm, and the hand is immersed for a few minutes in water at say 0°C, the limb, 5 to 10 minutes later, is found to be in an interesting state. Above the immersion line it is blue ; below the water line it is red, the line of junction between the two being sharply demarcated. The unimmersed skin is warm for the most part but, if closely observed, the skin over those veins that carry blood from the hand is perceptibly colder than that which surrounds it. The cold blood from the hand is passing very slowly up the veins of the arm. This coldness spreads so slowly in such veins as the radial, that its progress is to be detected only by repeated examination, and may reach the elbow as

late as 8 minutes after immersion begins. Immediately above the water line, and for a few inches, the venous blood may be sufficiently cold to reduce the overlying skin temperature to 10°C (Fig. 40) ; this band of skin is then reddened and stands out prominently against the general blue background. Yet although the circulation is of this extreme slowness, the hand remains bright red in colour (*171*).*

To take an extreme instance, let the hand be immersed in water at 10°C and, when it is fully reddened, let the circulation be arrested in the limb, the hand remaining under water. The red colour of the hand is maintained for 5 or more minutes, and cyanosis develops so slowly that it is inconspicuous even at the end of 10 minutes (*171, see 97 also*). If water at higher temperatures is used, and a reddened hand in which the circulation has been arrested is plunged into it, cyanosis develops the more quickly according as the temperature is higher. In hot water the hand becomes deeply cyanosed in a few seconds.

Blue response to cold.

Conspicuous cyanosis of the skin in response to cold is an abnormal reaction. If the skin is exposed locally to, and is maintained at, a given temperature, the natural rate of blood flow associated with such temperature is in general sufficient to meet the tissue needs. When the skin temperature falls, the rate of blood flow through it falls, but so does the rate of oxygen exchange with the tissues ; when skin temperature rises, so do both the blood flow and the rate of oxygen exchange. The balance is held, or is more than held, and blood flow remains adequate at low temperatures, from 15° to 10°C and downwards, and at high temperatures from 25° to 30°C and upwards. Goldschmidt and Light (*97*) examined the gaseous content of the blood from the superficial veins of the arm, the latter being previously immersed in water at various temperatures. They found that the oxygen content is raised when the arm is rendered cold, the change being most conspicuous as the bath temperature is lowered from about 17° to 6°C.

A slight cyanosis of the skin is sometimes seen as a preliminary and transient event after immersing a warm hand in water at 10°C. It is more frequent at 15°C, and at this temperature may be relatively persistent in parts of the skin immersed. It is more usual still to see slight cyanosis of the skin after its immersion at temperatures around 20 to 25° (*171*). The cyanotic skin of hands exposed to the atmosphere in the cold months of the year, are usually found to have a temperature of between 20° and 25°C. Goldschmidt and Light's data (*their Fig. 2*) show the oxygen saturation of the venous blood of the arm to be in general lowest at a bath temperature of about 24°,

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* Thus it is not always true to say that if the venous pressure is raised to 70 mm., a red skin indicates arteriolar dilatation, though the only exception to this statement is the instance of skin in which oxygen exchange is almost at a standstill (see page 45).

a value in close accord with our observations.*   When the bath temperature rises to about 34°, the oxygen content of the venous blood becomes normal, and from this point upwards, and especially over the range 40° to 46° it rises rapidly until it comes almost to an arterial value (*97, 189*).

There is a particular temperature range, namely, 15° to 25°C approximately, over which blood flow tends to be deficient in meeting the full needs of the skin.   The conception may be expressed diagrammatically (Fig. 41).

Fig. 41.   A diagram intended to illustrate the relation between oxygen exchange from blood to tissue and the rate of blood flow, while the skin is at various temperatures. The temperature range over which cyanosis is distinct in normal people is indicated by shading.

The upper curve throughout is intended to represent rates of blood flow in the skin at various temperatures, the lower curve to represent the rates at which oxygen is given up to the tissues. When the first curve lies above the second, it is supposed that the tissue needs are fully supplied ; when the curves come together, it is supposed that the blood flow is not fully adequate. These two curves are not considered accurately to represent the events in all their details ; to construct such we should require far more accurate knowledge

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* Their values are variable. It is to be remembered that the blood analysed comes, not only from the skin, but also in greater or lesser (and unknown) quantity from deeper tissues that do not experience the temperature change to the same extent.

than we possess. The diagram does assume that the curve of oxygen exchange begins to rise before the curve of blood flow, and that ultimately the latter is rising more steeply than the former.

If, in a series of tests of the effect of temperature on colour, we impose on the veins of the normal subject a pressure of 70 mm. Hg, this procedure will in each test impede the circulation, and the curve of blood flow will fall lower throughout ; doubtless the interference will also alter the form of the curve, its later parts being more affected absolutely than the earlier ones. Experience shows that in these circumstances cyanosis, as opposed to redness, begins usually to be manifest at about 15°C and is progressive until a temperature of about 40° to 43°C is reached ; from that point onwards redness of the hand again appears.

Response by paling.

This reaction is the least manifest of any, unless we include the paling of skin previously reddened by warmth on immersing it in colder water. If the skin of the arm at a temperature of about 32°C is plunged into water at 30°, 25°, or 20°C, usually it is difficult to be sure of any very appreciable change of general colour, unless, at the last named temperature, a slight pallor or cyanotic tint develops (*171*) ; in similar circumstances it is stated that the vessels are seen microscopically to become smaller (*35, 43*). At lower temperatures the minute vessels normally do not contract ; on the contrary, they expand, and a pink or red colour is in general assumed as has been stated previously. Whitening of the skin, as opposed to slight paling, in response to cold is an abnormality, or occurs only in special conditions. These conditions are not fully determined or understood ; possibly conspicuous pallor in response to cold is sometimes reflex ; it is also seen occasionally when skin reddened by heat is brought into water at from 30° to 34°C.

Skin that is strikingly pale under conditions that can be regarded as normal is in general found to be warm or hot ; it is skin to which the arterioles are open, but in which the minute vessels have a high tone.

Causes of local reddening.

As has been seen, when the skin is stroked, or when it is lightly frozen, a local reddening results and constitutes the sole visible reaction, but if the stimulus is made a little stronger, a manifest surrounding flare is added. The flare is due to a local reflex, itself dependent upon the liberation in the skin of H-substance, to which local reddening is also ascribed. From such observations it is to be concluded that when, through such injury, the H-substance is liberated, the concentration in which this will act upon the vessels locally is less than that adequate to set up a manifest flare. So, when it is found that local reddening comes first at skin surface temperatures of about 36° to 38°C (page 141), that the flare becomes manifest at about

43° to 44°C, and that the wheal and the blister appear about 51° to 52°C (see page 57) ; then we have ascertained that a typical series of reactions occurs over a comparatively small range of surface temperature. The minimal temperatures for local reddening and for flare are remarkably close to each other. We thus possess most suggestive evidence that the initial and familiar reddening of the skin upon its immersion in hot water, is the first of a series leading up to the more frank manifestations of heat injury, the flare, the wheal and the blister. In view of this argument it becomes impossible without clear supporting evidence to accept as a conclusion the older view that the vessel wall dilates as a *direct* response to warmth and heat ; such evidence is not forthcoming ; on the contrary, evidence accumulates against the idea that heat exerts this direct influence.

The two arms are immersed in water at 41° to 42°C and are there held still for 2 to 3 minutes ; they become reddened to the water lines. The circulation to one is arrested and both are at once withdrawn and plunged more deeply into water at 20°C. After an interval of usually 4 or 6 minutes the heat hyperæmia has disappeared from the arm in which the circulation is intact. The other arm is now released and, when the reactive hyperæmia consequent upon the release of the obstructed circulation has faded away, the heat hyperæmia on this arm usually becomes visible and remains so for a period of about 6 to 8 or more minutes from the release (*171*). In other words the disappearance of the heat hyperæmia is delayed by the arrest of the circulation for a period at least equal to the duration of the circulatory arrest. Thus, the fact that the skin lies exposed to a low temperature during the period of circulatory arrest has no great effect on the reaction to previous heating. It seems impossible, therefore, to regard the skin redness produced by a short immersion in water at 42°C as due to the direct effect of heat on the vessels, or to attribute it to anything else but excessive accumulation of vasodilator substances in the tissue spaces (*171*).

An even more convincing experiment, since it is free from the objection that the two arms are treated differently in respect of circulatory arrest, is as follows :—the two arms are immersed in water at 41° to 42°C for 2 minutes, are taken out and reimmersed more deeply, the one in water at 32° to 34°C, the other at 20° to 25°C. The fading of the lines of heat hyperæmia on the two arms is then watched and timed. Now, if the heat hyperæmia is due to a direct effect of warmth on the vessel walls, then this effect should be counteracted more quickly by the colder bath. The reverse is actually and very definitely the case ; the heat redness disappears in about 2 to 3 minutes from the arm in the warmer bath, in about 5 to 8 minutes from the arm in the colder bath. Thus, the speediest way to abolish skin redness induced by heating is to reimmerse the skin in water that is somewhat, but not very decidedly, colder ; the reason being that in the warmer water the circulation to the skin is greater and the products of metabolism, accumulated during the previous heating, are washed away more quickly (*171*).

Thus it would appear that reddening of the skin in response to warming or heating is not due to a direct effect of increased temperature on the walls of the minute vessels, but is brought about indirectly through the liberation of vasodilator substances in the skin.* When the temperature applied is moderate, we are forced to regard these metabolites as normal ones. It is of course possible that, when the temperature reaches a certain point in an ascending scale, the composition of the released substances begins to alter, normal metabolites giving place to those of injury. There is no evidence that this is so, and a simpler and at present adequate conception is that the severer and more abnormal reactions to higher temperatures are to be regarded as expressing a release of abnormal quantities of normal substances, rather than as expressing a release of abnormal substances (*171*). Briefly, the redness of the skin produced by warmth and heat may be said to be due to H-substance, and these observations lend support to the view that the H-substance of injury is a normal metabolite.

In contrast to the observations upon redness produced by heat, are those on that produced by cold. We have immersed the arms in cold water (10° to 13°C) until red (5 to 10 minutes), have then arrested the circulation in one and have reimmersed both in water more deeply at about 30°C ; but we have been unable in this way to delay the disappearance of the redness of cold, the skin of the two arms being found equal in colour when, after release, the reactive hyperæmia has passed away from the arm to which the circulation has been stopped previously (*171*). If the arms, similarly reddened by cold, are reimmersed more deeply, the one in water at 32°C, the other at 25°C, the redness disappears very rapidly from the former (in 1 to 3 minutes) more slowly from the latter (in 5 to 10 minutes). These results are clearly compatible with simple and direct temperature effects (*171*).

To sum up the reactions of the minute or endothelial vessels to moderate temperatures, it may be said that the only truly *direct* influence that we are now entitled to postulate, is one in which heat increases and cold lessens their tone. Temperature change, however, exerts an *indirect* influence, by altering the amount of vasodilator substances held in the tissue spaces ; heat increases and cold diminishes their concentration and thus leads to vasodilatation and to vasoconstriction, respectively.

Thus temperature, directly or indirectly, exerts two influences that are in conflict. Starting from normal skin temperature and passing up the temperature scale, the predominant influence is the indirect one ; the vessels dilate and the skin reddens in response to the free release of metabolites ; at the higher temperatures such metabolites concentrate sufficiently to produce the flare, the wheal and the blister. Starting from the same point

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* An observation by Grant and myself (*164*), in seeming conflict with the conclusion here reached, is dealt with elsewhere (*171*).

and passing down the scale, the tissue metabolites become reduced and the skin may be seen to pale a little ; but, as temperatures fall lower, the change in metabolic activity soon becomes less in its degree and importance, and the direct or paralytic influence of cold begins to predominate, dilating the vessels and so reddening the skin. This predominance of the direct effect continues until temperatures are reached that are low enough to damage the cellular tissues, for example by solidifying them ; in these circumstances the flare, wheal and blister again appear, as an indirect effect.

CHAPTER XI.

REACTIVE HYPERÆMIA.

IT has long been familiar to surgeons, who use the tourniquet or the Esmarch's bandage, that if the arteries to a limb are completely obstructed for some while and are then released, the skin that these vessels supply flushes to a vivid red colour. A convenient method of demonstrating the reaction is to use the pneumatic armlet, applying it to the upper arm and raising the pressure in it abruptly far above the systolic blood pressure and rendering the limb below it pulseless. If the pressure is released in 10 minutes and the armlet is removed, the bright flush of what is now termed a "reactive hyperæmia" quickly pervades the limb, and continues, though gradually declining in intensity, for several minutes.

Early descriptions of this phenomenon are to be found in the writings of Cohnheim (*50*) and Lister (*178*). It was investigated extensively towards the close of the last century by Bier (*22, 23*) who exploded the hypothesis previously and widely held, that the reaction is due to paralysis of the vasomotor nerves to the limb, by demonstrating that the reaction is obtained equally well if all the nerves to the limb have been severed previously. In amputating limbs, Bier cut through all the nerves and flesh, leaving the main artery and vein alone intact ; occlusion of the artery and its subsequent release was followed by the usual hyperæmia. Section of a nerve trunk, carrying vasoconstrictor fibres to the blood vessels of the skin, may be followed by a slight flushing of the skin (see page 208) but this slight flush is of much less intensity than that of "reactive hyperæmia" and soon disappears. Pressure that is sufficient to arrest the circulation to the limb is altogether insufficient to cause paralysis or even paresis of the limb nerves, which long survive and retain their functions when deprived of blood supply ; thus sensation does not usually begin to be impaired in the arm to which the circulation has stopped until 15 or more minutes have elapsed.

Grant and I have shown that the reaction is independent of local nervous reflexes also, for it occurs equally well when the nerves to the skin have completely degenerated. In the reaction, skin that has long been completely anæsthetic, as a result of old standing lesions of the main nerves, flushes to precisely the same extent as does adjacent skin, which still possesses normal innervation (*164*).

Bier believed reactive hyperæmia to be a response of the vessels to the inrush of arterial blood, but his view, though supported by experiments

devised by Zak (*271*), has been dealt with destructively by Krogh (*137*, see also *127* and *214*), who places a different and more correct interpretation upon experiments that will be discussed in Chapter XXI.

Reactive hyperæmia, as we shall see, is shown most intensely when the circulation has been arrested ; it is also shown after the circulation has been merely hindered. In investigating the phenomenon in man, the method most relevant to the skin circulation is to observe the colour changes in the skin. A more accurate way of displaying the time relations of the effects is perhaps to study limb volume ; this method, however, includes the changes in the deeper lying tissues, for these are also involved.

Before proceeding to relate the effects of arresting the circulation by arterial occlusion, and the lesser effects of obstructing the blood stream by
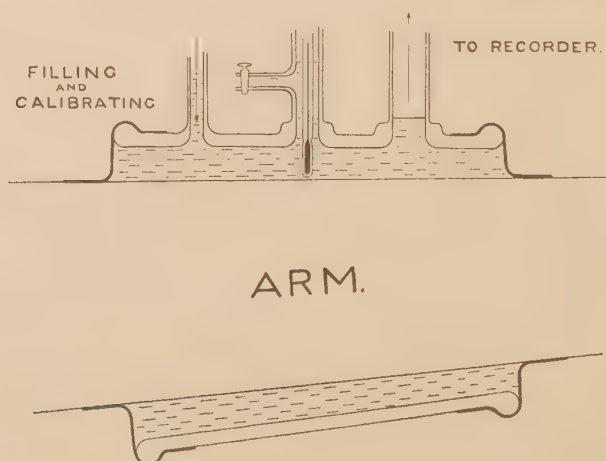
Fig. 42 (×) Plethysmograph for forearm.

imposing pressure on the veins, the volumetric method will be described briefly, since this is applicable in studying both series of effects.

Volumetric method. In taking volume curves from the human arm a plethysmograph devised by Grant and myself (*165*) is serviceable. The instrument (Fig. 42) has the form of a truncated cone and is applied to the middle of the forearm, the wrist and elbow being unenclosed. The two ends of the plethysmograph are fitted with rubber cuffs and the arm is inserted through these. The rubber cuffs rest against and grip the skin, enough to render the apparatus airtight and no more. The volume of the tissue enclosed varies from about 400 to 700 c.c.. The wrist and elbow are rested and firmly wedged by sandbags, to support and hold the limb. The sandbags are arranged at the bottom of a bath of water, the temperature of which is controlled. The plethysmograph is fitted with a thermometer, with an inlet tube for filling it with water and for calibration, and with a wide and vertical outlet tube in which the water is allowed to rise to form a short column.

Records are taken of the movements of the water meniscus in the outlet tube by means of air transmission to bellows recorders of different sensitivities. Any increase in the volume of the limb displaces water into the outlet tube and moves the recording instrument. A recorder yielding about 1 centimeter excursion to each 5 c.c. of fluid displaced suits most purposes. Appreciable movements of the fingers or of the whole arm have little effect upon this plethysmograph ; no movement of sufficient magnitude to distort the record can occur, without the subject being at once conscious of it.

The observations are conducted in a still and warm room (temp. 21 ͯ to 23°C) ; the subject rests comfortably in a reclining posture for a half hour with the arm in plethysmograph and water bath, at a desired and constant temperature, before the corresponding observations begin. At the end of this time the volume record should be an almost perfectly straight line, except for the small excursions of pulse beat and respiration. The limb circulation can now be modified by armlets placed on the upper arm as far from the plethysmograph as space will permit * and the corresponding changes of volume, which the limb undergoes, are recorded graphically.

Effects following circulatory arrest.

It is generally believed that the longer the occlusion the greater is the duration of the subsequent hyperæmia (Cohnheim *50*), though with the exception of a few values given by Tomita (*245*) no statements of time are available. The relation is easy to see in the skin of an arm maintained at normal temperature. Grant and I placed the two arms in a bath of water at 33° and maintained them there for 15 to 20 minutes. One arm was now used as a control for colour, and the circulation to the other was arrested for various periods. The table on page 157 summarises the resultant reactions in three subjects.

Speaking approximately, the flush on release lasts half to three quarters as long as the arrest, rarely as long as the arrest ; the fraction is usually smaller when occlusion of the vessels is very prolonged. The ending of the reaction is difficult to time, fading, which is at first very rapid in all but long arrests, being at the end extremely slow. It is clear from such a table that the duration of the reaction does not reach its maximum after arrest lasting 10 minutes.

The same fact may be demonstrated very clearly in the following way. The circulation at the level of the centre of the forearm is stopped for 5 minutes : a second armlet is now placed on the upper arm, and is pumped to a high pressure, which is maintained for a further period of 10 minutes, the lower armlet being removed meanwhile. At the release of the upper cuff the whole arm flushes vividly, but in a short while the skin of the lower forearm, which has been deprived of circulation for 15 minutes, becomes quite definitely and

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* The precautions necessary in applying these armlets are discussed elsewhere (*165*).

Fig. 43. *Reactive hyperæmia.* ($\times \frac{1}{3}$ approx.). An armlet was wrapped
with care to avoid creases around the elbow of a subject whose systolic
blood pressure was 110 mm.Hg. The armlet pressure was raised to
140 mm.Hg, and maintained for 10 minutes ; it was then released,
the armlet at once removed and the arm photographed 1 minute
after the release. The uniform and deep flush of the whole arm,
below the line where the upper border of the cuff lay, is shown, as is
also the sharp junction between hyperæmic and non-hyperæmic areas.

Fig. 44. *Reactive hyperæmia lasting longer with longer occlusion.* An armlet
was applied to the forearm of the same subject and a pressure of 150 mm.
Hg applied for 10 minutes. The same pressure was now thrown into
a second armlet embracing the elbow, the lower armlet removed at
once, and the upper one retained to the end of the twentieth minute.
Thus, the circulation to the elbow region had been stopped for 10
minutes and that to the lower forearm for 20 minutes. The second
armlet was now removed. The whole arm flushed brightly below
the line at which the upper border of this last cuff had been applied ;
a deeper flush was soon visible below the line marking the upper
border of the first armlet. Two minutes from the release, the flush
was still brilliant on the lower forearm, but was fading on the skin
in the elbow region ; the contrast between the depth of flush over the
two areas of skin was conspicuous and is shown in this photograph.
The duration of the preliminary occlusion was made longer than that
stated in the text, so that the contrast might be more readily seen in
the photograph.

Fig. 43.   Fig. 44.

Time relations of the flush (values in mins. and secs.).

Arrest lasts.	Flush on release.	Fading begins.	Fading advanced.	Colour normal.
½ min.	Very faint or none.	...	...	...
1 „	Faint.	0,10 to 0,20	0,35 to 0,40	0,40 to 1,5
2 „	Faint to distinct.	0,12 to 0,20	0,40 to 1,30	1,30 to 2,10
5 „	Fairly bright.	0,20 to 0,25	1,5 to 2,10	2,45 to 5,15
10 „	Fairly bright to bright.	0,25 to 0,35	1,30 to 2,30	5,50 to 7,30
15 „	Bright to very bright.	0,30 to 0,45	2,5 to 3,20	7,45 to 8,30

sharply marked off by its greater depth of colour from that of the upper forearm, in which the standstill of circulation has been 5 minutes less in duration (Figs. 43 and 44, page 155). Arrests lasting 20 minutes or more are associated with a good deal of discomfort, with numbness and aching during the actual arrest, with intense tingling and sometimes with painful cramp soon after the release. Circulatory arrest lasting for hours is dangerous, being followed from time to time by permanent paralysis and other ill effects, as Volkmann and others (*29, 70, 257*) have shown; consequently they should not be attempted.

A small area of skin may be deprived of circulation for very long periods without discomfort or damage. If a rubber band, its ends heavily weighted, is hung over the dorsum of the wrist or over the shin, the limb resting horizontally, and if it is left in place for an hour or more, the hyperæmia following release is long lasting. Thus, pressure exerted in this way for 100 minutes was followed by a hyperæmia lasting for about 40 minutes.

The relations between the duration of arrest and of subsequent hyperæmia here described are important to arguments that follow in the next chapter. In animal experiments under anæsthetics similar relations are not always found (*96*); the changes actually occurring in man have therefore been corroborated volumetrically. Thus Fig. 45 shows the effect on limb volume

of releasing the circulation in a number of consecutive observations.* While the forearm lies in the plethysmograph, the pressure in an armlet on the upper arm is abruptly raised far above systolic blood pressure. The pulse beats are at once lost and the volume of the limb is written as a straight horizontal line ; the pressure is maintained for a given period of time and released, when the volume curve at once bounds upwards as here shown, the limb becoming engorged with blood. The curve rises to a summit and then gradually declines to its original base line as the reaction passes off. The lower records present the reactions yielded by 1, 2, 4 and 8 minutes of arrest respectively. Following arrest of 1 minute, the curve reaches its original base line in about 25 seconds ; after a 2 minute arrest the base line is reached in about 70 seconds ; after a 4 minute arrest the curve is still a little above its base line 120 seconds later ; after an 8 minute arrest it is still well above its base line 140 seconds later. A curve from the same subject displays a further prolongation of the reaction after 16 minutes of circulatory arrest.

In these curves it is also to be observed that the volume pulse increases hand in hand with the degree of the reaction ; it is maximal on the ascending line and summit of each curve and subsequently declines.

The broad results are manifest. The longer the arrest continues, the greater is the subsequent increase of volume and the longer does increased volume prevail. It is also evident that the maximal limb volume is reached at a later point after long than after short arrests, the times for the four lower curves of Fig. 45 being approximately 6, 6·5, 8 and 10 seconds, respectively, from below upwards.

The effects of very short arrests are illustrated by Fig. 46. The volume changes are so small in such experiments that more sensitive recording instruments must be used to display them. The figure shows six curves, taken in quick succession, by compressing and releasing the subclavian artery. Using this method, the curve does not remain horizontal, as in occlusion by armlet pressure, but falls below the base line as the vessels empty. On release it rises quickly, and passes beyond the original level to a height that varies with the length of occlusion. It is the rise above the original volume that constitutes the hyperæmia, and a rise can be demonstrated after arterial obstructions lasting no more than 5 seconds, providing that the limb is warmed, for this exaggerates the reaction. The rise, however, is minute. In the present illustration it amounts at 36°C to less than 1 c.c., the volume of limb tissue being 610 c.c..

From the shortest occlusions of 5 seconds to the longest of 16 minutes or more there is a continuous and steady increase in the subsequent reaction, as the figures here published sufficiently illustrate.

Inflow curves. The same volumetric apparatus has been used for another purpose (*165*), a possibility pointed out by Hewlett and

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* When such observations succeed each other, a suitable time should naturally intervene. This time should be at least the duration of the last period of arrest.

Fig. 45.   (× ⅔ approx.)   In the lower tracing four forearm volume curves of reactive hyperæmia are superimposed. They were produced by previously occluding the vessels of the upper arm for 1, 2, 4 and 8 minutes, respectively. Plethysmograph temperature 34°C.. Calibration in steps of 5 c.c. is shown on the index mark of this and subsequent tracings.   The upper tracing shows reactive hyperæmia following occlusion for 8 and 16 minutes, respectively. Plethysmograph temperature 32°C. ; these temperatures are marked at the right-hand top corner of these and all subsequent records. Arm volume, about 600 c.c.. These and all similar curves in the chapter read from left to right.
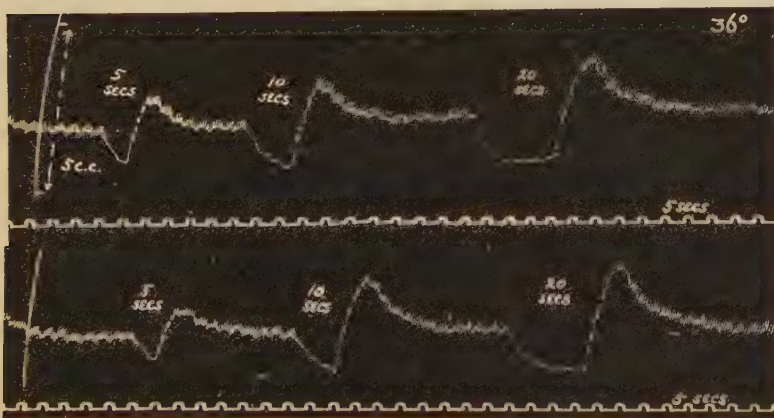
Fig. 46.   (× ⅘)   A series of six forearm volume curves taken in the order shown. The subclavian artery was obliterated for 5, 10 or 20 seconds and released. A more sensitive bellows recorder was used. Arm volume, 610 c.c..

Zwałuwenburg (*116*), namely, to study the rate at which blood flows into the arm. In this observation a pressure sufficient to impede the blood flow in the veins, but insufficient to interfere with that in the arteries, is thrown abruptly into the armlet on the upper arm. All the blood flowing into the forearm in these circumstances is retained there and the volume curve rises steeply ; the rate at which it rises measures the rate at which blood enters the limb. It will be clear that if the venous pressure is allowed to rise very far, it will impede the flow into the limb, and this is seen in the gradual rounding off of such curves as the limb swells. Only the early and straight phase of the curve should be used for measurement.

An example of a normal inflow curve is shown in the lowest record of Fig. 47. The pulse beats are seen in this curve throughout. Near the middle of the record a congesting pressure of 70 mm. Hg has been thrown on to the veins, to collect the blood in them, and the curve rises from that time very gradually but steadily ; the rate of inflow is equal to 4 c.c. of blood per 100 c.c. of tissue to the minute.

The remaining curves of this figure show abnormal rates of flow caused by the release of the arterial circulation, after arrest for $\frac{1}{2}$, $1\frac{1}{2}$, 5, and 15 minutes, respectively. These curves are obtained as follows :—the arteries to the limb are occluded by means of one armlet and, when this has been accomplished, a collecting pressure is thrown into a second armlet on the same arm. On releasing the first, blood rushes into the limb and is held there by the collecting armlet. In the present example, which is sufficiently representative, arrest of the circulation for the periods employed yields subsequent inflow rates of 15, 34, 49 and 55 c.c. per 100 c.c. per minute, the last being nearly 14 times * that of the normal inflow at the same temperature.

The subsidence of this increased flow may be studied by measuring inflow from minute to minute after the release, and an example is shown in Fig. 48. The rate of inflow is found to decline gradually during a period of from 3 to 5 minutes after releasing a circulation that has been arrested previously for 10 minutes.

The data given sufficiently indicate the general characters of the reaction and show the three methods of observation to agree substantially. This is important particularly in that the visual method takes cognisance of the skin only, while the two remaining methods apply to all the tissues of the limb. By each method the reaction is shown to vary in intensity and duration according to the length of the preceding circulatory arrest. Although it is impossible by either method precisely to time the end of the reaction, it has been made clear that the subsidence of volume, of rate of flow, and of

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* This value is exceptional, but a tenfold increase is not uncommon. It is to be remarked that the values apply to the arm as a whole and do not necessarily indicate corresponding values for the skin (see page 229). It is also probable that the actual rates of flow to the limbs are somewhat overestimated by this method since the first rush of blood after the arrest occurs into relatively empty arteries.
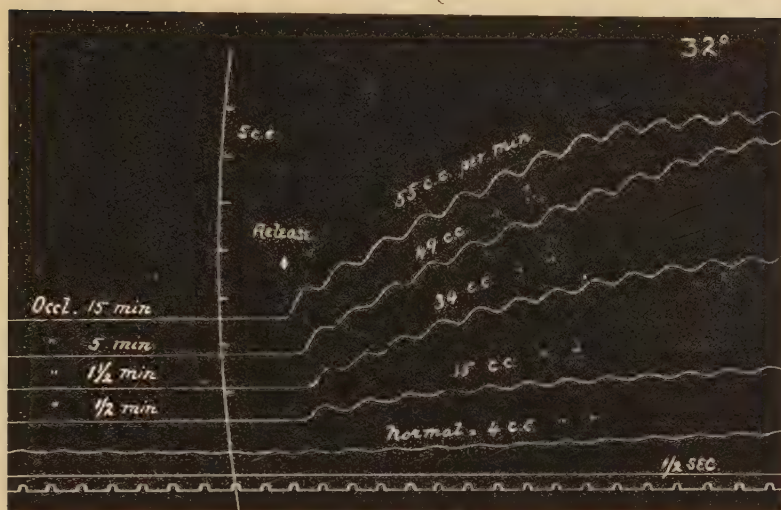
Fig. 47. ($\times \frac{4}{5}$) Syst. B. P. = 120 ; diast. = 90 mm. Hg. Five forearm volume curves showing the normal rate of inflow, and the rates on releasing the circulation arrested for $\frac{1}{2}$, 1, 5 and 15 minutes, respectively. The collecting pressure thrown on to the veins was 70 mm. Hg. The rates of inflow were 4, 15, 34, 49 and 55 c.c. per 100 c.c. of tissue per minute, respectively. Arm horizontal arm volume, 460 c.c.. Temperature of room, 21°C..
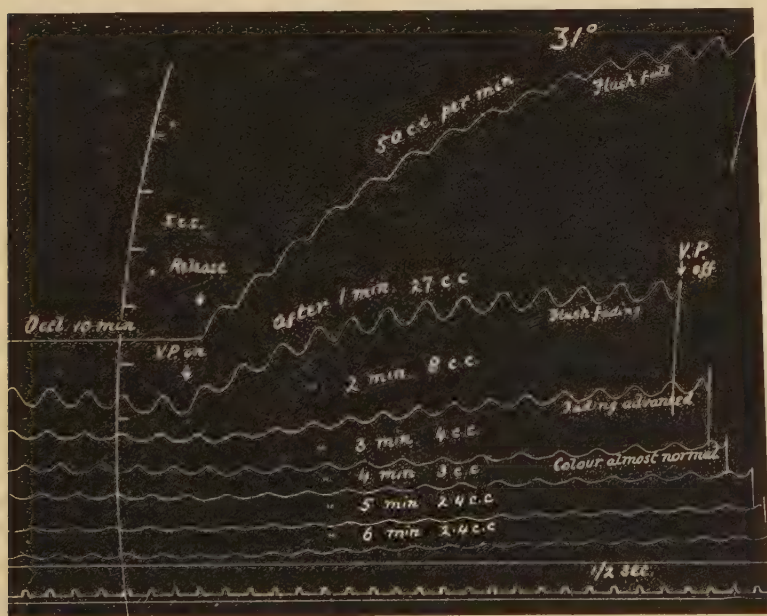
Fig. 48. ($\times \frac{2}{3}$) Syst. B. P. = 120 ; diast. = 80 mm. Hg. A series of seven inflow curves to the forearm. The first, the top, curve was obtained as was those of Fig. 47, the release coming after 10 minutes' arrest of the circulation. The remaining curves were each taken by releasing the original collecting pressure of 60 mm. Hg (at *V. P. off*) and reimposing it (*V. P. on*) at successive intervals of one minute, following the arterial release. The rate of inflow declines to normal, the values being approximately, 50, 27, 8, 4, 3, 2·4 and 2·4 c.c. per 100 c.c. of tissue per minute. At 5 minutes the inflow rate became constant. Arm horizontal ; arm volume, 560 c.c.. Temperature of room 22°C..

skin flush take place hand in hand within the limits of observational error (see remarks written on Fig. 48).

Such are the effects of arterial occlusion. The changes in colour, in limb volume and in blood flow are described in some detail, because almost precisely similar methods are employed in studying the effects of venous obstruction. This also results, as Grant and I discovered, in reactive hyperæmia but, because the limb has been congested and the hyperæmia is less distinct, its detection and interpretation are not so easy ; nevertheless, as we shall see, each and all of the phenomena previously described are reproduced and are recognisable.

Effects following venous congestion.

The colour changes that follow venous congestion and its release will be considered at a later stage. We will consider first the volume change in the limb.

Now when the circulation is arrested by throwing a high pressure on the upper arm, the natural volume of the forearm does not alter ; this natural volume is held until the release and so a pure curve of hyperæmia is then obtained. On the other hand, when the veins are obstructed, the arm swells as blood accumulates in it. It is necessary, in comparing volume curves taken in the two circumstances, to remember this difference and its effects on the release curves.

If a pressure of 25 or 30 mm. Hg is thrown onto the veins of the upper arm, the forearm swells (Fig. 49). The volume curve runs quickly, in 15 to 20 seconds, to a shoulder and then takes a horizontal course. Swelling is due to blood being caught up in the veins and is soon complete ; the venous pressure soon rises to cuff pressure. If higher pressures, 40 to 60 mm. Hg, are thrown onto the veins, the pressure in them also rises quickly to the cuff pressure, the rise being full in about 30 seconds (see page 20) ; but the volume curve, after rising at first steeply, does not run horizontally but continues to mount gradually. This second upward movement results in part from distension of the vessels, a distension due, not to increasing pressure within them, but to loss of tone in their walls ; it is due in small part to the formation of tissue œdema, and the last though very slow is continuous (*165*).

The effects observed during the period of raised venous pressure, and at its release, are several. Thus, when a pressure of 40 to 70 mm. Hg is thrown onto the veins and is maintained there, the lever recording limb volume soon writes along an almost horizontal line ; it is true that there is a slight upward inclination, but the swelling is a very slow one. Usually within a period of 2 minutes, often earlier, it is definitely to be seen that the volume pulse is increasing ; the increase is a very gradual one, so gradual that its starting point is not ascertainable. At the end of 10 or 15 minutes the increased amplitude is usually maximal and is then unmistakable

(Fig. 50). This increase in the size of the volume pulse forms a first suggestion that venous engorgement causes dilatation of the vessels on the arterial side.
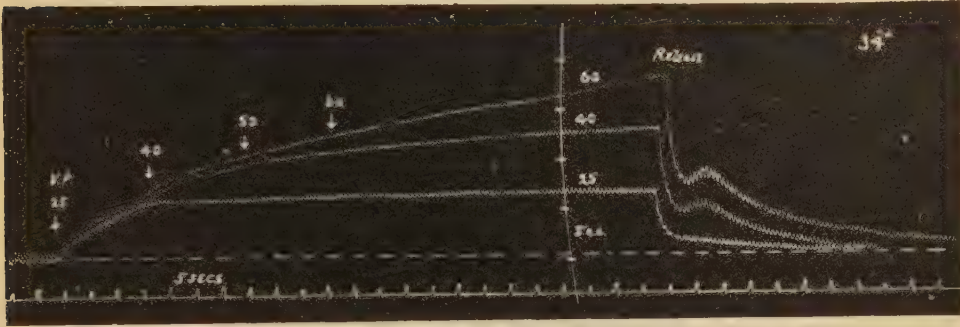
Fig. 49. (× ⅔ approx.). Forearm volume curves. The lowest curve shows the effect of throwing a pressure of 25 mm. Hg onto the veins of the upper arm. The curve rises quickly to a shoulder and then runs horizontally until, at the end of 2 minutes, the pressure is released, when the curve speedily falls to its original base line. The middle curve is similar except that the pressure is raised to 40 mm. at 20 seconds. The top curve is similar to the middle except that the pressure has been further raised to 50 and finally to 60 mm.. Arm volume, about 600 c.c.

At the release of congestion, the curve falls at first swiftly and then more gradually towards its original base line, as the congested veins empty themselves. When low pressures (20 to 30 mm.) have been used, the release curve is a simple one ; but if higher venous pressures have been attained the smooth and gradual descent is broken by a hesitation or by a distinct rise (Fig. 49). The greater the pressure used and, within limits, the longer it is maintained, the more prominent is this hump on the line of descent (Fig. 51).

This hump corresponds to the curves of rising volume displayed in Fig. 45, page 159, but here the event is complicated by simultaneous emptying of the congested veins.

The natural line that would be followed in the case of simple emptying through the veins is readily obtained for comparison in the following way. A venous congestion at a given pressure is maintained for a chosen time, and the usual humped curve is obtained at the release. The observation is now repeated, but, immediately before the cuff pressure is released, the subclavian artery is obliterated where it crosses the first rib ; at the release of the cuff the volume now falls in a steady and rapid sweep and becomes horizontal. A pair of curves obtained in this fashion is shown in Fig. 52. The comparison permits us to obtain a more exact idea of the superimposed curve of arterial filling. Emptying of the vessels through the veins produces a smooth and
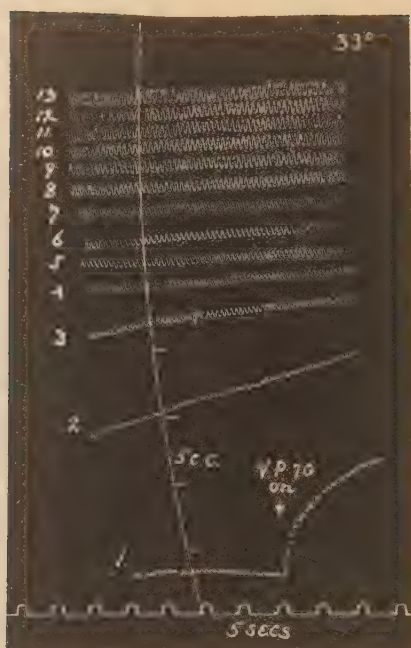
Fig. 50. Syst. B. P. = 118 ; diast. = 80 mm. Hg.   Curve *1* shows the first effect on forearm volume of throwing a pressure of 70 mm. Hg onto the veins of the upper arm.   This curve is continued, without altering drum or lever level, in the remaining strips (*2* to *13*), the curves being taken at intervals of 1 minute precisely, by moving back the drum.   Arm volume, 600 c.c..
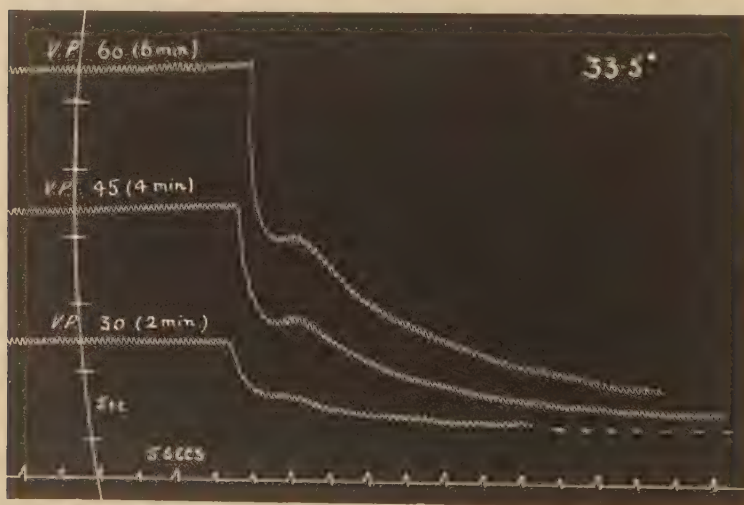
Fig. 51.   (× $\frac{4}{5}$) Three forearm volume curves showing the effect of releasing various venous pressures, namely 30 mm. (imposed for 2 minutes), 45 mm. (imposed for 4 minutes) and 60 mm. (imposed for 6 minutes).   Arm volume about 600 c.c..

steep descent ; a subtraction of this curve from the humped curve, will yield a curve indicating roughly the rate at which blood enters the limb from the arteries. It increases rapidly at first and then slowly declines.

A rising hump means that, during the rise, blood is entering the limb from the arteries more rapidly than it is leaving it from the veins ; now the venous outflow at this phase is increased beyond normal, owing to the raised venous pressure ; it follows, therefore, that arterial inflow must also be above normal at this phase. A rising hump may be interpreted therefore as meaning a peripheral resistance lower than normal. A lowered peripheral resistance with venous pressure normal would signify vasodilatation ; a lowered resistance, with venous pressure raised, as it is at the phase when the hump is written, can only mean a considerable vasodilatation and one occurring on the arterial side.
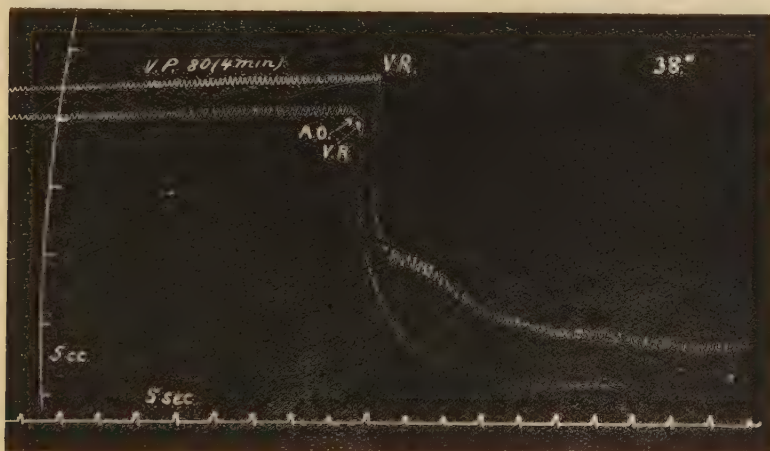
Fig. 52. (× ⅘) Syst. B. P. = 125 ; diast. = 85 mm. Hg. Forearm volume curves. The venous pressure was raised to 80 mm. Hg and maintained for 4 minutes. The release is shown in the top curve (*V.R.*). The bottom curve is similar, except that immediately before the release of venous pressure, the subclavian artery was obliterated (*A.O.*) and maintained so. Arm volume, 585 c.c..

It might be conjectured that this vasodilatation is passive, being consequent on previous distension of the congested vessels, and in no part active. Evidence showing that this is not the case has been obtained from the volume curves themselves (*165*); but, as this is intricate, I omit it and am content to cite simple and in themselves convincing experiments bearing on this point a little later.

Meanwhile it is to be noted as shown by volumetric analysis, that circulatory arrest and venous congestion produce the same effects. Each

yields a vasodilatation, which is at its height at the release, which soon declines speedily and then more gradually. A venous congestion to a high point, for 5 to 10 minutes, would seem to yield a curve of vasodilatation not dissimilar in amplitude and in duration to a somewhat shorter arterial occlusion. This conclusion is substantiated by measuring the rate of inflow.

Inflow curves. The veins are suitably engorged and congestion is maintained for a given period, at the end of which the pressure is abruptly released ; approximately five seconds later, and at a time when the steep fall in volume is over, and the hump is being inscribed, a collecting pressure is thrown into the armlet, and the corresponding inflow curve is obtained. The rate of inflow is greater, the higher the congesting pressure used (Fig. 53)
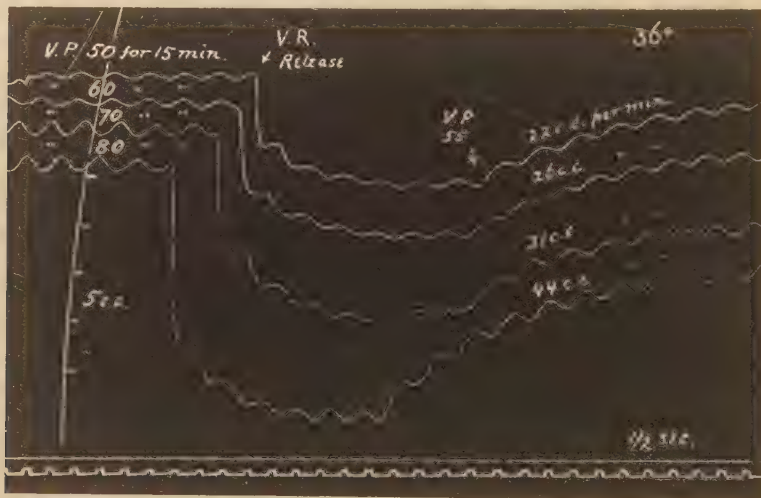
Fig. 53. ($\times \frac{4}{5}$) Syst. B.P. = 125 ; diast. = 88 mm. Hg. Forearm volume curves, showing the effect of venous congestion on subsequent inflow. In the first curve the release of the veins (*V.R.*), congested to 50 mm. Hg for 15 minutes, is shown. Five seconds later a collecting pressure (55 mm. Hg) is thrown onto the veins, and the curve rises at an inclination from which the inflow rate is calculated. The remaining curves are similar, except that congesting pressure of 60, 70 and 80 mm. were employed. The inflow rates for the four curves were, approximately, 22, 26, 31 and 44 c.c. per 100 c.c. of tissue per minute, respectively. The normal inflow rate was 10 to 12 c.c.. Arm volume 610 c.c..

and, within limits, the longer this pressure has been applied. Using pressures approaching or reaching diastolic pressure, and maintaining these for 10 to 15 minutes, a threefold or fourfold increase in flow may be obtained. The increase is of an order not dissimilar to that obtained by arterial occlusion, though the effects of the latter, continued for similar times, are greater and last longer. It seems inconceivable that passive distention of the small

vessels could so reduce peripheral resistance as to bring about flows of this magnitude. The inflow curve is taken at a time when the hump on the curve of declining volume is inscribed, and at a phase when venous pressure is above normal ; the effect of this increased pressure, in so far as it acts, is to lower the rate of inflow and partly to conceal the dilatation of the small vessels, when inflow is used to gauge the extent to which these are open (*165*).

Colour changes. These are of most importance to us, because their evidence applies solely to the skin. The release of venous congestion is quickly followed by a bright arterial flush, which displaces the cyanotic colour of the skin and which declines hand in hand with the fall of limb volume and, as nearly as can be ascertained, to the decline in inflow rate ; the flush varies with the grade and duration of previous congestion.

The colour changes, studied in special circumstances, have the further value of resolving once and for all the question of active as opposed to passive dilatation. We enclose the hand and wrist completely in a glass container, the mouth of which is closed by a tubular rubber sleeve, through which the
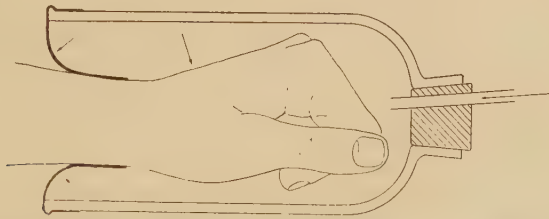
Fig. 54. (× ⅓) Apparatus used for impeding the circulation in the hand, by throwing pressure onto the veins, without distending them. Pressure is thrown into the chamber through the inlet tube shown to the right.

hand is introduced. The sleeve is inverted and rests lightly on the vaselined wrist (Fig. 54). Pressure in the bottle is abruptly raised and, being exerted on the margins of the inverted sleeve, seals the vessel. Alternatively, the sleeve is not inverted, but lightly grasps the forearm and is there secured by a pneumatic armlet wound around it and pumped to a desired pressure. Using the first method, a pressure of 70 mm. Hg thrown into the bottle is exerted equally upon the wrist and hand ; using the second method, a pressure of 70 mm. is thrown into the bottle, and a pressure just sufficient to close the leak (about 75 mm.) onto the lower forearm. The results obtained are substantially the same. A pressure of about 70 mm. Hg is imposed on the veins that leave the wrist, and venous pressure in the hand rises to this value ; but the veins of the hand do not swell, they are supported by the pressure in the bottle. Thus, passive distention is avoided. But, while venous pressure has been raised in this experiment, arterial pressure is left unin-fluenced, and the purely mechanical influence of the procedure must clearly

be towards a greatly diminished blood flow. If the pressure is maintained for suitable periods (5 to 10 minutes) the release is followed by a bright arterial flush of the hand ; and in general the higher the pressure used and the longer it is maintained, the brighter and more lasting is this flush. The after-effects on skin colour are similar to those obtained by uncomplicated congestion of the hand. To control the method properly, two containers, similarly fitted, are used, one hand being inserted into each, and these lie side by side. In this way any fallacy arising from a rise of temperature in the air surrounding an enclosed hand is avoided ; moreover the colour of the hands may be compared, as may also the distension of their veins. The first method described does not cause the veins to swell, they remain unchanged in size or diminish slightly. Using the second method, in which the sealing pressure is under separate control, the degree to which the veins swell may be regulated to a nicety (*165*).

These observations conclusively show that active dilatation of the vessels is the effective cause of the hyperæmia that is seen when a limb previously congested is released. The exaggerated volume pulse (Fig. 50) during the phase of congestion, and the ascertained vasodilatation within a few seconds of release, are explained if we conclude that the active vasodilatation occurs gradually during the period of congestion and is at its height at the release. This view is substantiated by the appearance of a hand enclosed in a pressure bottle. If the hand is engorged by throwing a pressure of 70 mm. on the forearm only, within a minute the skin of the hand is manifestly cyanosed. If the pressure in the veins is raised by simply raising the pressure in the container, no cyanosis is manifested ; the colour of the hand and that of the control remain alike. If the forearm is first compressed and cyanosis of the hand induced, and the pressure in the container is then raised almost equally high, the engorgement of the hand at once disappears, but the hand remains at first cyanotic ; as it is watched, the cyanotic tinge gradually vanishes and the natural colour becomes restored. If the pressure in the container is released at this stage, while the congesting pressure on the arm is maintained, the hand assumes at once an arterial colour which subsides and gives place to cyanosis again after a period of several minutes.

A still simpler but a cruder method of showing the same events is to place one armlet on the upper arm and another on the forearm and, through a Y tube, to pump each to 70 mm. Hg. This pressure is exerted for 5 minutes, by which time the arm is deeply congested and cyanosed. On quickly removing the armlet from the forearm, the skin here pressed upon is found to be of a natural colour, but quickly becomes arterial in tint ; this arterial colour fades away very slowly, but is ultimately displaced by a tint indistinguishable from that of the surrounding skin. The observation may be repeated by reimposing the pressure on the forearm.

These phenomena can be explained in one way only, namely, by active vasodilatation occurring during the period of raised venous pressure. When this pressure is first raised, the blood flow in the limb becomes retarded ;

as a consequence, a compensating vasodilatation comes early into play, and the flow to the hand improves.

The discharge of circulatory debt.

It has been shown that arrest of the circulation to the skin, or obstruction of the circulation such as is imposed by raised venous pressure, is followed by the display of a reactive hyperæmia, and that the extent and duration of this hyperæmia depend upon the extent to which the tissues have been deprived of blood and the duration of this deprivation. The reaction is one of high importance, being vital to the tissues concerned, as Roy and Graham Brown (*222*) were the first to point out ; it involves a mechanism by which tissues deprived of a proper blood supply tend to become repossessed of it. Bier emphasised its importance to the opening up of the collateral circulation in areas to which vessels have been blocked permanently.

In this mechanism is to be found a delicate regulator whereby the slightest and most local needs of the tissues are satisfied. It is manifestly a reaction that is brought into daily if not hourly play in various regions of the body. Whenever the body rests, parts of it are brought under pressure where it makes contact with its support. In sleep large areas of skin and underlying tissue are sufficiently pressed upon to render them wholly or partially anæmic ; similarly with the buttocks in sitting ; the circulation in parts of the soles of the feet is at a standstill in man in the erect posture. Evidently these local obstructions to the circulation often continue uninterruptedly for long periods of time. They are relieved in healthy people by movement, which, by changing the area of pressure, allows reactive hyperæmia to occur,* and the parts originally starved of blood are instantly flooded.

It is to be observed that the pressure that must be exerted on the skin, to produce subsequent hyperæmia, is far below arterial blood pressure. It is sufficient to impose a pressure that will close the minute vessels. If the arm is supported horizontally, the subject sitting, and pneumatic pressure is applied to the white skin of the upper arm for a period of 5 to 10 minutes, the minimal pressure required to produce a reaction that is just perceptible has been found to lie at 30 mm. Hg or a little more. If higher pressures are used, the reactions subsequently seen become more distinct, but they remain patchy, until such pressures as 65 to 85 mm., are employed. With these pressures, at which presumably the circulation to the skin is first brought to a complete standstill†, a full and uniform flush is obtained, indistinguishable in its brightness and its duration from that obtained by a pressure of 250 mm. Hg or more on the control arm. The pressure required lies some

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* In paraplegic subjects a soft mattress and frequent movement are essential to prevent the occurrence of bedsores.

† In a previous article (*165*), these observations were incorrectly interpreted.

30 to 40 mm. Hg below systolic pressure in the main artery of the limb, and is not far removed from that which is read as diastolic pressure. The following values exemplify the readings obtained :—

Subject.	Blood pressure		Minimal pressure producing full flush.
	systolic	diastolic	
1	105	75	65
2	122	75	83
3	118	72	87

Hyperæmia will similarly follow venous obstruction. Normally pressure is frequently exerted on venous tributaries from local territories when the body comes into firm contact with external objects. When a man wades or stands in deep water a pressure of as much as 70 or 80 mm.Hg may be exerted continuously on the veins of the calf ; such a pressure greatly exceeds that natural to the veins of the calf, providing the limbs are not flaccid. Again, the veins of the limbs are often obstructed by local muscular contractions. The veins entering the abdomen are pressed upon by contraction of the muscular abdominal walls, in many efforts that involve such acts as the carrying of heavy weights. Similarly, the venous system as a whole is congested by a rise of intrathoracic pressure, and this is also frequent in sustained effort. In disease, pressure by tumours or fibrotic tissue on veins coming from small or large territories is a frequent phenomenon ; general venous congestion occurs in most of those who die of cardiac failure. In all these states, the compensatory changes here described will come into play, locally or generally.

In all conditions, whether the obstruction is arterial or is venous, the subsequent flood that pours into the territory involved when the obstruction is removed is, as we have seen, proportioned to the needs of the tissue ; the accumulated debt to local metabolism is thus met and healthy equilibrium restored ; necrosis of the tissues is avoided.

CHAPTER XII.

REACTIVE HYPERÆMIÀ, THE MECHANISM INVOLVED.

WE proceed further to consider reactive hyperæmia and to discuss the mechanism provoking it.

Bayliss (*13*), who studied the reaction in animals, came to the conclusion that the arterioles increase in tone as a response to raised pressure within them, and decrease in tone when their arterial pressure is lowered, since smooth muscle responds to stretching by contraction. When the arteries to a limb are occluded the pressure within them falls, and this fall was thought to produce active relaxation of their muscular walls. Anrep (*4*) has criticised this hypothesis and has given reasons for doubting the interpretation placed on the corresponding experiments ; though, as has been said recently (*165*), Bayliss's explanation of reactive hyperæmia is not thereby placed out of court.

It will be well if we chiefly concentrate our attention upon reactive hyperæmia as it is observed in man, and this is the more advisible since, in attempting to explain it in the human subject, we should recognise that results obtained under the condition of animal experiment are not always apposite to man. The present is in fact a noteworthy illustration of this statement. It is perhaps impossible to measure the relevant quantities so precisely in man as in animals that are reduced by anæsthesia to perfect stillness and control. The disadvantage is offset however in other directions. It is the reaction in man himself of which we particularly require knowledge. Moreover in the human experiment the nutrient fluids bathing the limb are those natural to the limb and to the reaction, and this has not always been the case in animal experiment. Our observations are undertaken upon the unanæsthetised subject, the body as a whole is healthy and undisturbed, the general circulation is perfect, conditions rarely, if ever, realised in animal experiment, and yet probably essential to an elucidation of the full truth where such a delicate reaction is concerned.

While, as we have seen, reactive hyperæmia in man is prolonged and intensified by increasing the period of circulatory arrest, this is stated to be so only within comparatively short time periods in the case of anæsthetised animals (Goldblatt, *96*).* In fact this very peculiarity in the case of the

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* In anæsthetised cats, I have been unable to confirm this observation, judging by the duration of the cutaneous flush.

animal influenced Bayliss's conclusion ; it was unknown to this worker that the reaction is prolonged, by maintaining the preceding vascular occlusion, after the time at which the pressures within the vessels have become constant, a fact which could not be explained on his hypothesis. Further, the mechanical explanation does not cover what has now been demonstrated, namely, that a rise of venous pressure produces a similar and active vaso-dilatation, for in this instance the pressure within the vessels is not lowered, but is raised. These and other arguments (*165*) make it certain that reactive hyperæmia in the human subject is not due to the cause stated.

The central fact is that vasodilatation is always displayed if blood flow has previously been diminished, irrespective of a rise or fall of arterial pressure ; the reaction is evidently related in its degree to one factor only, namely, to the blood flow debt, which in general is the product of the amount by which flow is reduced and the time over which this reduction has been maintained.

The time at which vasodilatation occurs.

Roy and Brown (*222*) believed that vascular tone is lost *during* the period in which the tissues are deprived of blood ; others have expressed the same belief. Bier (*22 and 23*), however, concluded that the vessels widen in response to the inrush of arterial blood ; his interpretation of observations upon which he based this view has not proved acceptable ; nevertheless evidence for dilatation during the period of occlusion has scarcely seemed to be conclusive. The minute vessels of the skin, which give it a natural colour, do contract in places, when deprived of blood supply ; and the meaning of this con-traction is imperfectly understood (see Chapter XXI).

An observation by Krogh (*137*, see also *165*) is to be interpreted in the reverse sense. By pressure he obliterates the vessels in a small area of the rabbit's ear for some minutes, and then cuts off the circulation to the whole ear ; on releasing the local pressure this area is seen to flush. We have confirmed this observation upon the rabbit. A similar reaction is to be obtained with greater ease, and perhaps more conclusively, on the human skin. Firm pressure is exerted on a small area of the skin of the forearm for a period of 10 minutes ; a pressure of 50 mm. Hg is then thrown upon the veins of the upper arm and, when congestion has become established, the vessels in the upper arm are obliterated. The local pressure on the forearm is now released, and the corresponding area is seen to be white ; but colour suffuses through it from its edges ; its colour darkens as more blood enters it, until it stands out as an area of intense engorgement against the bluish tint of the surrounding skin. If an area beside it is blanched by similar though transient pressure, the colour returns, but in returning does not surpass that of the surrounding skin in depth. On releasing the circulation to the whole arm, general hyperæmia follows, though it is more intense and long lasting in the area longer deprived of circulation ; this area of lasting

hyperæmia corresponds exactly to that which showed intense engorgement while the circulation was still obstructed.

These observations favour the view that the vessels lose their tone during the period of the occlusion. Very definite evidence that the vessels of the limb as a whole have already lost their tone is to be found in the curves of rate of inflow. The increased rate of flow that is seen so conspicuously after long occlusions is manifested by the first pulse beat to follow release. Although the amount of blood remaining in the arteries must be substantially the same, whether the occlusion has been for 1, 2 or 5 minutes, the steepness of the first volume pulse is conspicuously greater after a longer occlusion, and the amount of blood entering the arm at that beat is conspicuously greater (see Fig. 47 page 161). That could only be the case if peripheral resistance were already greatly decreased at the instant of release, and such a reduction of resistance must be ascribed to toneless vessel walls. In harmony with this conclusion is the evidence derived from the increased volume pulse in simple congestion, and from the immediate and long continued reddening of the congested hand when a supporting pressure is released (page 167).

Lastly, Kendrew (*129*) has recently performed a crucial experiment in my laboratory. He connects a vein of the forearm in a normal man with a citrate manometer by means of a cannula introduced into its lumen, and records the pressure changes in this vein from the instant the circulation to the arm is stopped. The first change is a brief increase while some of the blood, standing under pressure in the arteries, becomes transferred to the veins and establishes pressure equilibrium ; a decrease now sets in and is continued steadily during the period of circulatory arrest.* The form and extent of this fall is such as can be accounted for only by gradual and continuous relaxation of the vessels of the limbs.

Thus there is no room for doubting that the hyperæmia that appears on releasing an obstruction to the circulation is due to a vasodilatation occurring during the phase of obstruction. The phenomena witnessed at the release are brought about by a pre-existing vasodilatation, which begins to decline at the release or very shortly afterwards.

The vessels actively involved in the skin reaction.

The skin becomes flushed in reactive hyperæmia because, as in all flushes of the skin, the minute vessels become distended, as may readily be seen microscopically. The reason for this distention is to be found in active involvement of the minute vessels themselves, and the reddening is mainly produced in this way, just as it is in the red line that follows stroking.

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* A similar experiment was performed on the dog by Bier (*23*), who ensured as did Kendrew that there should be no escape of blood through the veins of the bones, but failed to place a correct interpretation upon the result. The decrease of pressure occurs too rapidly and is too profound to be accounted for by escape of œdema fluid from the vessels.

The tests that prove this are similar to those already described in the case of the red line (Chapter III). When the circulation to a limb has been arrested by means of an armlet, then, on releasing the pressure, hyperæmia of the skin develops up to a line that is defined with notable sharpness; this line marks the proximal margin of the region compressed (Figs. 43 and 44, page 155). That it marks this margin precisely may be shown by encircling the arm with a tensely drawn and broad rubber band, or by exerting pressure on the skin on one side of the arm by means of a similar band, the position of the margin of the rubber band being marked on the skin while it is in position. When the band is removed after many minutes, the hyperæmia extends to the line previously marked but never passes measurably beyond it; were it to pass a millimetre beyond, this extension would be recognisable in the test. From this description it is manifest that no vessels that are sufficiently large to distribute blood to more than a few square millimetres of skin participate materially in the reaction; the hyperæmia is due to dilatation of vessels of the smallest orders.

Active involvement of the capillaries and minute venules is shown by an experiment previously described. Firm and elastic pressure is exerted on a few square centimetres of the skin of the forearm, and is maintained; at the end of 10 minutes the whole arm is congested by means of an armlet and, when the veins have filled, its vessels are occluded. At this stage we have to deal with an arm in which the circulation has ceased, but which contains a considerable amount of blood under pressure in its vessels. If pressed upon with a finger the skin is blanched mechanically and, on release, the vessels of the blanched area quickly fill from surrounding vessels, the area so treated soon becoming indistinguishable from the surrounding skin. When the area of skin submitted to long pressure is released in similar circumstances, it also fills with venous blood from its margin, but it becomes of a dark violaceous colour, contrasting conspicuously with the slightly cyanosed tinge of the surrounding skin. This deep colour is due to active relaxation of the walls of the minute vessels; they cannot dilate passively while no blood is circulating in the limb (*165*).

The increased blood flow through the vessels of the skin in reactive hyperæmia may be seen microscopically and is also readily shown by a congestion test. The circulation in the hand and wrist is stopped by means of a pressure cuff; a second cuff is placed on the upper arm and pumped to 60 or 70 mm. Hg pressure. At the end of 5 or 6 minutes the turgid arm has assumed a deep blue colour. If the lower cuff is now removed, the hand and wrist develop a long lasting hyperæmia, the corresponding skin area becoming red and contrasting with the cyanosed skin of the forearm; the line dividing the two colours is sharply defined at the level where the upper margin of the lower cuff previously rested (*165*). The same effect follows if the lower armlet has been applied at a pressure of 60 or 70 mm., as we have seen. Increased flow in the reactive hyperæmia of man cannot be demonstrated thermometrically, however, a matter further discussed in Chapter XVI.

These observations seem to implicate the arterioles in the reaction, though, as previously inferred, they can be only of the smallest orders.

It is impossible to exclude a slight reaction of arterioles of a larger order than the terminal arterioles and those of the subpapillary plexus, though there is no present evidence that such are involved.

Other than those named, the only vessels that are definitely known to react are the subcutaneous veins. These are increased in size at the height of the reaction, and this is due to something more than passive distension. During the early period of hyperæmia, as Kendrew (*129*) has shown, there may or may not be a little rise of venous pressure, such as would passively distend the veins ; but distension also occurs if the internal pressure in the veins is maintained at a constant point, a very necessary precaution in using the diameters of veins as a sign of loss of tone in their walls. The veins are first congested by a fixed pressure of 50 mm. Hg for a period of 3 minutes and the breadth of a given vein is measured, or the veins on the dorsum of the hand are photographed (Figs. 55 and 56, page 177). After allowing an interval for recovery, the vessels to the limb are occluded for 5 or 10 minutes ; they are then released, while a pressure of 50 mm. Hg is soon reimposed on the veins. In a half minute the measurement is repeated or a second photograph is taken. A distinct increase in the size of the veins, which under this procedure signifies loss of venous tone, is detected by this method.

To sum up, although it is true that the subcutaneous veins relax, it is quite clear that the reactive hyperæmia as it affects the human skin is due chiefly to active dilatation of the minute vessels. Thus, the vessels chiefly concerned in the reaction are vessels the walls of which are essentially endothelial ; the reaction is confined, mainly at all events, to vessels through which, judging from their structure, interchange between blood and tissue fluids occurs. This in itself suggests that the reaction results from a local chemical change connected with tissue metabolism. The reaction is independent of nerve control, central or local, as we have seen.

Two views of a chemical action may be held, the one that the vessel wall responds to an abnormality of the intravascular fluid or blood, the other that it responds to an abnormality of the extravascular or tissue fluid ; either of these may be supposed to arise from deficient blood flow, for deficient blood flow implies either a deficiency of some substance or substances that the blood brings normally to the tissue, or the failure of the blood to carry away some product or products of tissue metabolism. Many possibilities suggest themselves ; we are in a position to discuss a few briefly and **profitably.**

Figs. 55 and 56.   (× ⅗).   *Tone of veins decreased by circulatory arrest*. The
   lower photograph shows a hand in which the veins have been main-
   tained congested for 3 minutes at 50 mm. Hg.   After an interval
   for recovery the vessels of the upper arm were occluded for 10 minutes,
   released and then congested by reimposing the pressure of 50 mm.
   upon the veins.   They became more distended, as is seen in the
   companion photograph.
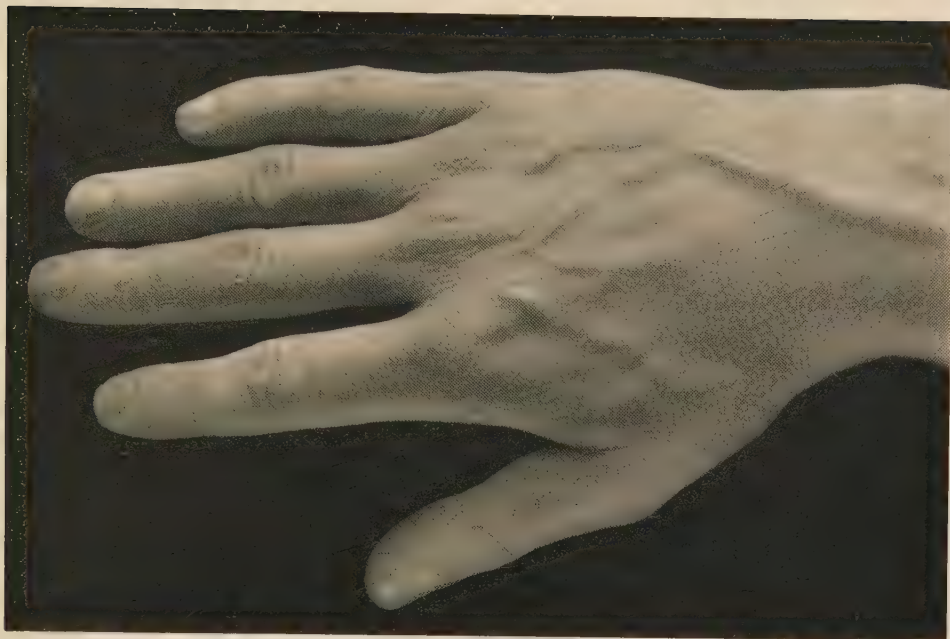
Fig. 55.

Fig. 56.

CHEMICAL AGENCIES.

Blood gases.

The possibility of a varying reaction to arterial and to venous blood has led many observers to test the effects of oxygen, of carbon dioxide and other weak acids, upon the vessels (*4, 91, 134, 225, 226*) ; the results of these experiments are in general consistent, and indicate that acids dilate the vessels. These experiments almost always involve perfusion of the vessels and other gross interferences ; in a delicate reaction of the kind, any change of the natural nutrient fluid may introduce serious fallacies ; however carefully a perfusate is built up, it cannot be regarded as equivalent to natural blood ; the very shedding of blood alters its constitution. Investigations of the reaction of the vessels to various fluids perfused through them, even though these contain red blood corpuscles, are beset with difficulties and with sources of error. To discuss such work in detail would not here be appropriate ; it will suffice to state that such perfusion experiments have failed to solve the problem in which we are interested.

It is manifest that neither a deficiency of oxygen nor an accumulation of carbon dioxide or other weak acids in the blood that lies within the vessels can possibly form the direct stimulus ; were that so the reaction would always be fleeting, the blood being at once replaced by the flood of the reactive hyperæmia. It is likewise improbable that an accumulation in the tissue spaces of substances as diffusible as volatile and weak acids, can be held to account for a hyperæmia lasting 10, 15 minutes or more, since this hyperæmia would rapidly cause the substances to be removed.

The influence of pituitary hormone.

Krogh (*137*) believes that reactive hyperæmia, as this occurs in the frog, may be due to the absence of a pituitary hormone, which hormone he regards as responsible for normal capillary tone. It is supposed that, when the circulation is brought to a standstill, the normal pituitary content of the blood locked up in the arm becomes reduced, and that the vessels of the part thereupon lose their tone and are ready to expand. It is known that extract of pituitary gland, when injected intravenously or intradermally, exercises a conspicuous effect on human skin capillaries, producing general or local blanching (Sacks *223*). It is not a difficult matter to test Krogh's hypothesis in so far as it could apply to reactive hyperæmia in man.

If a drop of pituitary extract is placed on the forearm and the skin is pricked through it with a needle, a small area of intense blanching soon appears and remains for an hour or more. If a series of white spots is produced in this way, and a reactive hyperæmia is then induced in the same arm, the little blanched areas remain and stand out in vivid contrast to the red skin. From this observation it is clear that if a sufficient amount of pituitary extract is introduced, it is capable of maintaining so high a tone

in the walls of the small vessels that a reactive hyperæmia is without effect on them.

The undiluted extract is a powerful one, too powerful for our purpose. It is diluted with normal saline solution until, when pricked into the skin, it yields little blanched areas that are just distinctly perceptible. The dilution required is usually about 100 times. The effect of reactive hyperæmia following a 5 or 10 minute arrest of the circulation, upon these faintly paled areas is now observed ; they participate in the hyperæmia and become indistinguishable from the surrounding skin. Usually, it is true, some of the areas remain distinguishable and are not completely lost in the general flush, though they become pinker in colour ; these are the areas that were originally paler than their neighbours. Now it might be suggested that the washing out of the faint white spots, produced by pituitary, is due to destruction of the substance during the period of occlusion or to its removal during the period of hyperæmia. This is not the case, for the pale areas are visible until the hyperæmia comes, and they reappear when it subsides. So far, therefore, as the vessels involved by the pituitary extract are concerned, it is clear that during the stage of hyperæmia their flushing is not due to a lack of pituitary tone ; they are supplied throughout with an excess of pituitary substance.

A final argument remains. It is possible that the pituitary extract, so introduced, affects the capillaries only, that the arterioles escape its influence, and that in the stage of hyperæmia lack of pituitary in the last named vessels dilates them and raises the pressure in the capillaries so far that these dilate passively despite their pituitary tone.

To test this possibility a different procedure is adopted. Grant and I (*165*) introduced pituitary extract into our own general circulations so that all classes of vessels might come under its influence. By introducing 1/30 or 1/20 of a c.c., intravenously, conspicuous blanching of the facial skin, usually accompanied by perceptible blanching of the skin of the arms, is obtained. Arrest of the circulation to a limb is followed in subjects so treated by a vivid hyperæmia of the skin, a hyperæmia that is seemingly as intense as in control observations ; but because there is an excess of pituitary substance in the circulating blood, the hyperæmia is of shorter duration than is that which is similarly brought about in the same subject when no pituitary extract has been introduced. To render this observation compatible with Krogh's view we see only one line of argument, namely, the possibility that the excess of pituitary substance present in the arm at the time of the circulatory arrest is destroyed during the period of arrest. Unlikely as this idea seemed to be, it has been tested.

A wide armlet is placed over the elbow joint, so that there may be no possibility of collateral or bone anastomsis with the lower arm, and its pressure is raised above 250 mm. Hg. At once an intravenous injection of pituitary extract is given into the general circulation. In 20 or 30 seconds the face of the subject is conspicuously blanched. At the height of the reaction, 30 to 45 seconds after the injection, the circulation to the control

arm is stopped. The two arms are now without circulation, and they differ from each other in that one has received pituitary extract through the blood stream, while the other has not. They are so maintained until 7 minutes have elapsed from the injection, when they are released simultaneously. Hyperæmia develops equally in the skin of the two arms, but it fades more quickly in the arm that has received pituitary substance. Thus, it is shown that the pituitary substance introduced into this arm is not destroyed, but that a material quantity of it remains in the arm during the period of circulatory arrest and during the subsequent reaction. Despite this excess of pituitary, the skin flushes, and flushes with an intensity equal to that of the control arm. It will be observed that this arm is deprived of circulating blood for a slightly shorter period than is that into which no pituitary has been allowed to enter before occlusion ; this shortening by 30 or 45 seconds of an arrest of 7 minutes' duration, however, has no appreciable influence upon the subsequent vascular reaction, as has been shown clearly by suitable control observations, undertaken either immediately before the main observations or after all sign of pituitary pallor has vanished.

Thus an excess of pituitary extract in the skin, or in the circulation, shortens reactive hyperæmia in the skin, but does not abolish it. Even though the excess of pituitary is retained in the skin throughout the reaction, hyperæmia occurs. The hyperæmia cannot be ascribed in these circumstances to lack of pituitary tone.* Goldblatt comes to the same conclusion from his experiments on animals (*96*).

There is strong evidence, to speak more generally, against reactive hyperæmia being due *directly* to the lack of any substance normally brought to it by the blood, namely, the duration of the long reactions. In the skin, the reaction may last for half an hour or more and, during the whole of this time, the vessel walls are constantly and excessively bathed internally by blood containing all its normal constituents. It is scarcely possible to admit that vasoconstrictor substances brought to the territory in normal concentration but increased amount, could fail to produce their full reaction for such time periods as these. Arguing in a similar way, the accumulation of vasodilator substances *within the minute blood vessels* during the period of stagnation, may also be excluded ; for such substances would be removed almost instantly when the circulation became restored. We turn therefore to the alternative, namely, the presence of metabolites in the tissue spaces.

The accumulation of metabolites in the tissue spaces.

The view that tissue metabolites may be the responsible agents was first put forward by Roy and Brown (*222*) and has recently been advocated by Anrep (*4*). The last worker has cited certain experiments on animals, and

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* That it may contribute slightly towards an ordinary reactive hyperæmia cannot be excluded, since some or all of the pituitary hormone, that may be supposed to be acting on the vessels at the time of the circulatory arrest, may very possibly be destroyed *in situ* before the circulation is released.

these are interpreted as demonstrating vasodilator substances returning from the affected territory ; but it has been pointed out that they are open to another and simpler explanation (*165*). On the contrary, an experiment on the human skin seemingly shows that vasodilator substances are not passed into the blood vessels during the period of circulatory arrest, at all events that they do not there accumulate in sufficient concentration easily to be demonstrable, or to be effective in producing hyperæmia.

An Esmarch's bandage is wound spirally around the hand and forearm, depleting it of blood up to a pneumatic cuff (*1* in Fig. 57), the pressure in which is now raised to a point far above systolic pressure. The bandage is removed and the blanched forearm and hand exposed ; the empty veins are to act as a reservoir. When 10 minutes have elapsed, the pressure in cuff *1* is reduced until it lies just above the known systolic pressure of the subject, who now, by briefly and forcibly expiring, forces a single jet of blood through the cuff. Little practice is required to drive an isolated pulse beat through the cuff. The effort is repeated every ten seconds, and thus a very slow percolation of blood through the capillaries is obtained. The slow percolation of blood through the vessels favours diffusion of the supposed vasodilator substances, accumulated in the tissue spaces during the 10 minute arrest, into this blood to an unusually high concentration ; the blood collects in the empty veins. When a sufficiency has been caught up, and this happens in the space of about 5 minutes, this blood is transferred to a new vascular territory.

The transference is affected as follows. Another cuff (*3*) is placed high on the upper arm ; a third cuff (*2*) completely overlaps the edges of cuff *1* and *3* and covers the portion of skin that lies between them. Cuff *2*, and immediately afterwards cuff *3*, is forced to 200 mm. pressure and cuffs *1* and *2* are at once removed. The skin so exposed (areas *B* and *C*) contains little or no blood, area *A* is turgid with stagnant blood. The arm is held up enough to allow this blood, which it is desired to test, to percolate into the skin of area *C*. The skin of this area suffuses quickly and deeply ; it is allowed to remain so for varying periods up to 5 minutes, when the last cuff *3* is removed. Now the skin of regions *C* and *D* has been treated as follows :—each has been depleted of blood and deprived of circulation for say 5 minutes, each, therefore, will as a result display hyperæmia on release ; but into *C* blood from *A* has been introduced for the greater part of the time. If this transferred blood contains vasodilator substances, their effect should be added and the hyperæmia on release should be more vivid and lasting in area *C* than in area *D*. In point of fact this is not the case, the hyperæmia that appears is equal over *C* and *D* and lasts no longer in the former than in the latter. Meanwhile areas *A* and *B*, so long deprived of circulation, experience equally the usual vivid and long lasting hyperæmia. It seems clear therefore that there can be no appreciable concentration of substances in blood passing even very slowly through tissues previously long deprived of circulation (*165*).

The observations suggest that any substance that may be responsible for reactive hyperæmia does not easily diffuse out into the vessels ; an idea compatible with the reaction that follows simple prolonged arrest of the limb circulation ; for, although after the release the circulation is greatly increased in the limb, and for many minutes the walls of the small vessels are freely bathed by blood that is arterial in character, the reaction persists for a long while. A substance of relatively low diffusibility and formed in the tissue spaces, rather than confined to the vessels or their walls, would seem alone to harmonise with the facts. Although CO_2 may be regarded as tending to produce vasodilatation,* yet because of its diffusibility it is highly improbable that this is the chief metabolite concerned in the reaction.
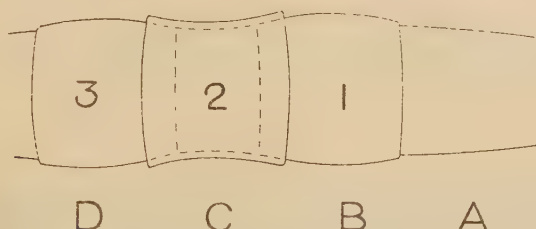
Fig. 57. To illustrate the method of transferring blood from one part of the arm to the skin of another, by means of three pressure cuffs.

Bayliss (*16*) urged that, since vasodilatation occurs after so short an arrest as 8 seconds, he found it difficult to believe that deprivation of blood flow for that period can cause an appreciable accumulation of metabolites in a resting limb. An arterial occlusion of 5 seconds suffices, as we have seen, to produce a subsequent increase of limb volume in man, though the reaction is minute. Since there is a continued and steady increase in the reaction as occlusion is prolonged, it is hardly to be doubted that the shortest and longest reactions are fundamentally alike. It is to be observed in this connection that deprivation of the brain of its blood supply for a period as short as 5 seconds so profoundly disturbs this organ that unconsciousness supervenes, a loss of function difficult to explain except on a metabolic basis.

Nature of the vasodilator substance. The observations and arguments put forward in the preceding pages direct our attention to the tissue spaces, and lead towards the belief that a vasodilator substance is there liberated and is responsible for widening of the vessels. Once this view is accepted, we are forced to assume that the responsible substance is a normal metabolite, for, as we have seen, a perceptible reaction can be shown in the limb to which the circulation has been arrested for so brief a period as 5 seconds. It is scarcely conceivable that the character of tissue metabolism alters in

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* The human skin when damp and exposed to pure CO_2, soon exhibits a recognisable hyperæmia, but this passes away quickly when the skin is exposed to air.

such a short period of time ; it is readily conceivable that normal metabolites continue to form but are not removed at a normal rate. Further, it would be gratuitous to assume that between the mechanisms underlying the subsequent hyperæmias of a short and of a long circulatory arrest, there is a fundamental difference ; it is simpler and safer to assume a gradual accumulation of a single vasodilator substance to explain a gradually increasing reaction.

Evidence of a distinct and more direct kind will be brought in the succeeding chapter to show that such a regulator of the peripheral circulation is in fact constantly in process of formation. Given this conclusion, then the accumulation of the substance during short periods of circulatory arrest becomes inevitable as a conception. I conclude therefore that reactive hyperæmia is due to the liberation of a normal metabolite in the tissue spaces and, from previous evidence, that this metabolite is non-volatile and is but slowly diffusible.
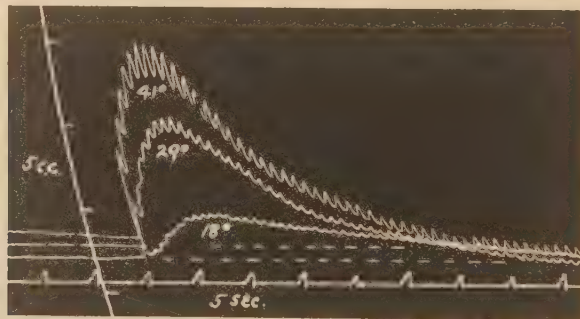
Fig. 58.   Three curves of forearm volume, following the release of the circulation in each case after a 2-minute period of arrest. The curves were obtained after the limb had been for half an hour at one of the corresponding temperatures, namely 18°, 29° and 41°C, respectively ; and the records show the increasing reaction with higher temperatures. It is to be remarked that the base lines of the three curves do not really correspond, they have been brought together so that the differences in reaction may be shown more clearly ; with a higher temperature, the vessels of the limb contain more blood at the instant of arrest.

In dealing in Chapter X with the effects of warmth on the skin, it has been concluded on independent evidence that local reddening is due to the accumulation of normal metabolites in the tissue spaces. These are naturally considered to be the same metabolites as are here postulated ; their production is expedited by increased temperature. Here it is to be remarked that the degree of vascular dilatation produced by arresting the circulation to the limb is intimately dependent upon the temperature of the limb within the plethysmograph. The higher the temperature, the greater is the reaction

(Fig. 58). This in itself suggests that the dilatation is dependent upon the rate at which metabolism occurs in the tissues.*

In the same chapter it has been shown that there is a gradual transition between the reaction of the skin to warmth and to heat, the latter bringing about, not only local redness, but the remaining parts of the triple response. Further, it has been pointed out that the reactions to the higher temperatures are sufficiently explained on the same basis as is the reaction to lower temperature, and that it is unnecessary to assume the release first of normal and later of abnormal metabolites. It becomes of interest to inquire therefore if the stimulus produced by circulatory arrest, known already to be cumulative as the period of arrest is prolonged, culminates in the full phenomena of triple response.

Cohnheim (*50*) noticed many years ago that, if the circulation has long been cut off from the rabbit's ear and is then released, manifest œdema follows. Similarly, increased permeability of the vessel walls appears from time to time after a long application of an Esmarch's bandage. In a patient under my care many years ago, arrest of the blood flow to the arm, during a prolonged operation on the wrist, was rapidly followed by the appearance of numerous large blisters of the skin, similar to those resulting from extensive and severe scalding ; their distribution began at the line at which the tourniquet had been applied. Surgical colleagues tell me that they have seen a similar occurrence on many occasions (see also *70*) ; they have been inclined to attribute the blistering to infection of the skin, an explanation however for which there has been, I think, insufficient evidence. Blistering not uncommonly occurs in the skin of paraplegic patients, in whom the circulation to the skin over the sacrum has long been arrested by the pressure of the mattress upon which they lie ; it is one of the events that leads up to the well known " bedsore."

If a tight rubber band 5 mm. broad is placed around the wrist and is left in place for about 8 hours, the skin, robbed of its circulation by pressure, subsequently wheals along the line of the band ; a surrounding flare may become distinctly visible, a diffusion flush (see page 122) is usual and is often prominent. Thus, simple circulatory arrest may be interpreted as leading to the accumulation of H-substance in the skin. It is supposed that, in such arrest, the concentration of released substance rises very gradually in the tissue spaces, and there is also evidence that the rate of concentration declines as time elapses ; the duration of subsequent hyperæmia is not maintained in strict proportion to the duration of circulatory arrest, it is relatively less after prolonged arrest.

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* Although the reaction seen at the release is much fuller at the higher temperatures, it has not been shown to be of longer duration ; apparently its duration is little affected, a fact that is to be explained, however, by quicker removal of the substances concerned, since when temperature is raised blood flow becomes much increased.

There is another argument favouring the view that the vasodilatation of reactive hyperæmia is due to H-substance released. There is evidence that simple circulatory arrest produces, apart from coincident stimulation of the skin, relative refractoriness of the skin concerned. This evidence is somewhat intricate but seems on the whole clear (*164, 250*); if it is sound, it is clearly significant to and favours the present conclusion.

We have concluded that when the skin is deprived of blood, non-volatile metabolites accumulate slowly in the tissue spaces and that these lead to vasodilatation; it is further suggested that if these substances become sufficiently concentrated, they lead to the more pronounced effects seen in the usual triple response. The idea is that in the case of physical injuries, release in relatively high concentration is abrupt, whereas here it is slow; minor differences in the reaction are therefore to be expected, as has been explained in dealing with reactions of long latency in Chapter IX.

To sum up from the general standpoint, reactive hyperæmia illustrates how vasodilatation may be produced by normal metabolic substances. It also provides suggestive evidence that these normal metabolites, if gathered in sufficient concentration, will yield the further reactions of the triple response; in this respect therefore it supports an earlier contention that the H-substance is to be regarded as a normal metabolite.

CHAPTER XIII.

REGULATION OF BLOOD FLOW BY LOCAL PHYSIOLOGICAL METABOLITES.

THE idea that a substance liberated in the tissue spaces may locally control blood flow has been mooted on numerous occasions. Thus, Roy and Graham Brown (*222*) many years ago made the suggestion in studying the hyperæmia that follows anæmia in the frog's web (reactive hyperæmia). They wrote (*page 348*) of this hyperæmia that it "seems to us to throw much light on the manner in which the local circulation is carried on under normal conditions. It shews us that there is a local mechanism independent of the centres in the medulla and spinal cord by which the degree of dilation of the vessels is varied in accordance with the requirements of the tissues." And again :—" It is not difficult to imagine, that an increase in the chemico-vital changes of the tissue elements will have the same influence on the degree of dilation of the vessels as temporary anæmia. In both cases there will be a relative diminution of some of the constituents of the blood and a relative accumulation of the products of tissue change, one or both of which would probably, as in our experiment, stimulate the vessels to dilate." This view, in so far as it concerns reactive hyperæmia, is discussed at length in the last chapter ; recent work has much strengthened Roy and Brown's suggestion, but lays the emphasis, not upon a decrease of blood constituents, but upon accumulation of tissue products. Other chapters of this book have been devoted largely to the demonstration that vasodilatation, arising out of different forms of injury, likewise results from the liberation in the tissue spaces of a substance acting directly on the vessels and on the nerve endings of the local reflex arc. Evidence has also been adduced for a similar cause of the reddening that follows warming of the skin. Of recent years a noticeable trend of physiological opinion has been to revise the view that the central nervous system sends out vasodilator impulses, and to refer such vasodilatation to a peripheral and chemical stimulus. Thus Gaskell (*91*) was inclined to attribute the increased blood flow of working muscle to acid accumulation, and Markwalder and Starling (*186*) have suggested that vasodilatation of the coronary vessels may be brought about by changes in the metabolic activities of the heart muscle. Barcroft and his associates (*5, 6*) have expressed similar views in respect of vasodilatation in the submaxillary gland, be it awakened originally by nerve stimulation or otherwise.

Returning to the skin, I propose to examine first of all the condition of the vessels while the body is at rest and while the skin is unstimulated ; certain changes have been described in these circumstances, and these have been associated with views concerning the local regulation of blood flow. For that reason, and also because an understanding of local differences in the condition of the vessels forms a necessary preliminary to discussions in subsequent chapters, these differences will be examined here in some detail.

The subject may be introduced by references to the statements of past workers.

Ebbecke (75) states that when the surface of the hand of a susceptible subject is watched while exposed to strong sunlight, or otherwise warmed, whitish and red spots of a few millimetres diameter are to be seen. Prolonged and careful inspection of these reveals a spontaneous change in the condition of the vessels. The distinctness of the spot changes in an irregular rhythm about once a minute ; at one time bright red and white spots are sharply differentiated, at another the speckling seems to have disappeared, an occurrence explained by a corresponding change in the blood flow. He describes a second phenomenon, namely, a slight change in the form of the spots, scarcely fully accomplished within the space of 15 minutes. He compares the change to the movement of an amœba under the microscope and to the formation of light clouds in a still sky, and says it corresponds to the behaviour of the capillary circulation in the frog's foot, in which the blood flows now through this capillary, now through that, while others remain unused. In his discussion he calls attention to changing activities in secretory glands, in which active and inactive cells are found lying side by side.

Carrier (43) examined the capillaries of the dorsum of her own hand, and concludes that all the capillaries are not open together. According to this worker they are opening and closing continuously ; while all the vessels are not open at any one time, certain of the capillaries are almost always open while others open only occasionally. The opening and closing is stated to proceed very rapidly, so that a drawing made every three minutes shows a different field each time. She states that an inspection of several microscopic fields clearly shows what may be seen macroscopically, namely, that little areas a few millimetres in diameter, where only a few capillaries are open, alternate with fields in which most of them are open ; macroscopically these areas are said to correspond to the little spots that come and go on the hands.

These statements have been amplified by later writers and have grown in distinctness. Thus Krogh (137) says of the red and white spots that they may be continually changing in location, and Mackenzie (183) in writing of the similar but larger mottlings on the arms and legs, mottlings further discussed in Chapter XIX, states that in a few minutes a dark patch becomes pale and the pale patch dark. These are coupled with other statements on the changes in individual capillaries, and we are left with the definite view

that the capillaries of the skin are in a constant state of movement, individually and in groups, the mottling of the skin changing unceasingly.

The behaviour of the capillaries, and of the mottlings on the hand and limbs, has recently been re-examined closely (*161*), for they are matters of high importance to the problem that concerns local metabolic regulation of the circulation.

Mottling on the palms of the hands.

Little red and white spots constituting a mottling on the palms of the hands are clearly visible in very many people, young and old (Fig. 60, page 191). They are more prominent if the hands are well coloured, either as a result of warmth or cold, or if the venous pressure in the hands is high, as when the arm hangs down. If the palm of such a hand is closely watched, the whitish spots, as Ebbecke (*75*) states, will occasionally cloud over and the mottling then becomes much less intense. This is constantly to be borne in mind when the spots are watched individually, for when a whitish spot becomes less intense or disappears it is usually to be seen that its neighbours behave similarly.

A method which I have adopted is as follows. An area of the palm, about 2 to 4 cm. in diameter is chosen, and the outlines of the whitish mottlings are traced very gently on the skin with ink. The subsequent relation of the whitish areas to these lines is observed. Now, while outlining the whitish area in this way, it is found that there is room for appreciable error. The mottling is not simply of red and white, but of all intermediate shades of pink also; strictly speaking, therefore, it would be necessary in marking the contours to follow a certain shade of pink; but to do this accurately is impossible, particularly since a very slight change in colour during the process may materially alter the position at which the line should be drawn. It is safer, therefore, to neglect the finer shades and to draw the lines a little more boldly and with particular attention to the most distinct pale areas. If this is done, and the subject remains resting and undisturbed in a still warm room, the hand unmoved, occasional flushing of the hand as a whole, as might naturally be expected, is less in evidence. In these circumstances, the outlines of the individual whitish areas can be watched more satisfactorily. I have examined the hands of six separate subjects, including two children, in this way and am convinced that the red and white mottlings are for the most part very constant in position. It is here to be remarked that Ebbecke has not stated that, apart from general flushing of the skin, the red and white spots come and go or replace each other; this is to be gathered from more recent writings on the subject and these appear to me to be inconsistent with the actual facts. On many occasions I have watched areas including numbers of marked spots for hours at a time, and it is unusual to see any very decided change in the pattern displayed. Usually every whitish area that has been ringed at the start remains whitish at the end of several hours observation, and the contours of the spots are for the most part still represented as

Fig. 59. ($\times$ $\frac{1}{2}$). *Mottling.* The forearm of a young man presenting conspicuous mottling of colour. The pattern is of the usual type, a darker reticulation enclosing paler areas.

Fig. 60. ($\times$ $\frac{2}{3}$). *Mottling.* The hand of a healthy adult, showing characteristic mottling of colour over the palm and fingers. The speckled condition has been intensified by maintaining a pressure of 50 mm. Hg on the veins of the upper arm.

Fig. 59.

Fig. 60.

accurately as they were by the original outlines marked on the skin. When a white spot does exceptionally become pink or red, it usually does so in company with adjoining spots of the same order, and it is frequent to see the pallor return within these contours, the pale zone resuming its original outline or one not diverging greatly from it. Little shifts of the borders there may be, red encroaching a little on white or white on red ; these changes are more difficult accurately to determine or to exclude, but they are certainly inappreciable in most instances.

It is now to be added that there is little change from day to day. Many white spots on an area of my own left hand were lightly outlined in ink on six separate days, the guiding marks being furrows in the skin. These outlines were each made at 8 o'clock in the evening in a warm room, and on each occasion the hand was re-examined between 11 o'clock and midnight. During none of these evenings was there any really appreciable change in the distribution or form of the pale areas. On each occasion, a piece of oiled paper was laid on the hand, the outlines retraced on this and preserved for comparison with each other. The ink marks on the skin were scrubbed away and no precautions of any kind were taken to preserve the hand from friction, heat, cold, etc., in the long intervals. Four of these diagrams are published (Fig. 61). In examining these it is to be remembered that precision in originally outlining the spots is impossible and that errors, which are not negligible, are also introduced in retracing the lines on paper, and that their relation to each other is somewhat distorted in projecting them in this rough way onto a flat surface.

The contours traced on October the 18th and 19th are the same, except in minor detail ; to the left a curious and large Y shaped figure is almost accurately repeated, spot after spot is found in its original place. Seemingly some have enlarged a little, some have dwindled a little, a few have broken in two or two neighbouring spots have become confluent, some have altered their outlines. Many of these apparent changes in detail are unquestionably due to error in outlining, to the indeterminateness of the edges, and to errors in retracing. In the contours of October the 23rd, four days later, the changes are somewhat greater, in those of November the 20th, nearly a month later, they are greater still ; yet even after this long interval the general pattern is preserved, and many of the original areas can be identified without difficulty.

These diagrams by no means fully represent the relative fixity of the mottlings. The most satisfactory plan is to mark in the outlines with a dye and to leave the marks on the skin for future observation, but this is not always very feasible when it is desired to follow the outlines for many days or weeks. Eight spots of complex outline were marked on the palmar surface of a child's hand with gentian violet and the hand examined two days later. At the time the hand was found to be almost uniform in colour, but within five minutes, by placing it at a suitable level, each of these spots reappeared in identically its original position and form. I possess two photographs

of the palmar surface of my right hand, taken at a three weeks' interval, in which dozens of white spots are shown in exactly the same positions in the two photographs ; not only is the location constant in these instances, but the form is usually preserved with precision. I am now familiar with the contour and positions of many white spots on my own hands and, over a period of many months, these spots have been substantially unchanged under resting conditions.

Oct. 18.   Oct. 23.

Oct. 19.   Nov. 20.
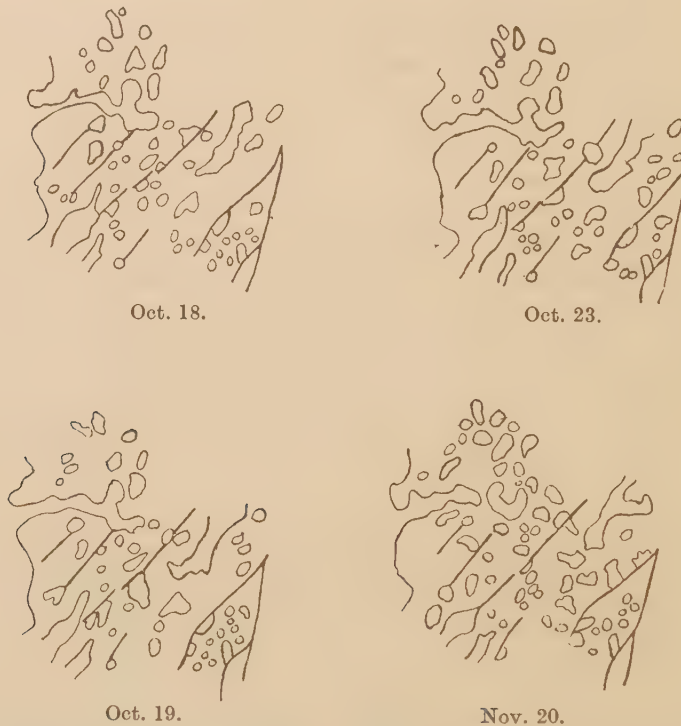
Fig. 61. ($\times \frac{3}{4}$). Four charts of the mottling on the hypothenar eminence of a hand, made independently on four separate days over a period of a month. The encircled areas were pale. The charts exaggerate the amount of change occurring in the actual location and form of the mottlings.

In two subjects a number of whitish spots has been outlined on the palm of the hand, and the hand has been soaked successively in water at temperatures of 15°, 20°, 25°, 30°, 35°, 40°, and 43°, each immersion lasting 5 minutes. The whitish areas became less distinct at the last two temperatures, but nearly all remained throughout as originally marked. Thus the form and position of the white spots is little influenced by moderate temperature changes.

They are little influenced by venous congestion or by temporary arrest of the circulation and its release. The spots are sensitive to friction or

stretching of the skin ; very sensitive in some subjects. Often the act of out-lining a spot is sufficient to abolish it ; movements of the fingers may have a similar effect. Much more often than not, a short further period of watching will be rewarded by the reappearance of the spots in their original places and form ; especially is this so if the level of the hand is changed to that at which the spots as a whole are most distinct. Thus, after a period of rest, a group of spots was outlined on the hand of a lad, who then resumed his manual work for a period of 2 hours. At the end of this time he was re-examined without rest and the spots seemed to have changed ; but after he had rested for 5 or 10 minutes every spot reappeared in its original place and in its exact or almost exact original form.

In brief, the skin of the hand presents certain small and *relatively fixed* territories of which the colour is paler than that of the surrounding skin. Such variations as occur or seem to occur in these territories are explained, so it seems to me, in one of the following ways. They diminish in size, in form and in number when the hand flushes as a whole. They show similar changes in response to friction or stretching of the skin, and here the changes are not necessarily or usually simultaneous over the skin as a whole.

Provided the hand is kept for a reasonable time under given and favourable conditions before it is observed, and provided that the spots are originally outlined when they are conspicuous and numerous, it is easily determined that the mottling does not come and go in a haphazard or fluctuating manner, but that it is governed more definitely ; there is a funda-mental pattern, which is maintained, or to which, if changes occur, there is a constant tendency to revert within narrow limits.

Mottling on the limbs.

There are similar though larger mottlings on the skin of the limbs and trunk of many people, a condition often described as *cutis marmorata* (Fig. 59, page 191). The mottling consists of paler areas of irregular outline, themselves encircled by reticulations of darker colour ; it has been studied by the same methods. The methods are subject to the errors previously mentioned, though the chief error usually arises here from the indefiniteness of the outlines. In no instance of conspicuous mottling out of seven studied has there been an appreciable change in the contours, during a period of one or several hours' watching, the limb being maintained at rest.

Fig 62 reproduces two tracings taken at a four days' interval during which no precautions were taken to safeguard the skin ; this was on a forearm that had been marked in six places with silver nitrate, as guiding points. Areas that correspond in the three diagrams are numbered accordingly. The general location of white areas 1, 2 and 3 is unaltered and the spots have preserved their crescentic forms ; 5 has seemingly altered in its form and in its size, 6 has seemingly become divided. The remainder have apparently altered in lesser or greater degree. Here, as in the case of the

hand, there may be seeming change in detail from day to day, but at all events it is clear that the general pattern is preserved in notable degree. Change in outline, when it seems to occur, is due largely if not in chief part, to variation in the choice of contour in charting. This same area of mottling was subsequently outlined with gentian violet, the shades of colour being also indicated, and was examined three or more times daily for 4 days. Over the whole of the period there was scarcely any appreciable change in a single red or pale area, though no precautions to safeguard the skin were

Nov. 20.   Nov. 24.
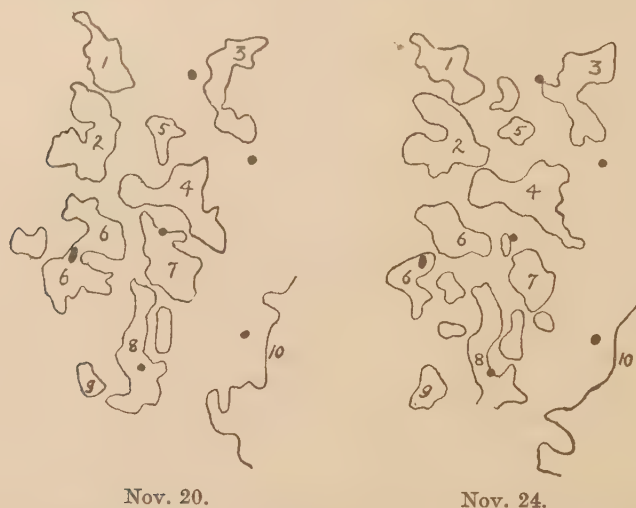
Fig. 62. (× ¾). Two charts of the mottling on a forearm taken at an interval of four days. The numbered outlines represent pale areas. The black spots are silver nitrate marks on the skin.

adopted. Five other subjects have been examined in the same way and with similar results. I possess two photographs of a mottled arm taken at a three weeks' interval and these show the mottlings to be substantially unaltered.

These broad mottlings on the skin resist much interference. Repeatedly the circulation to the limb has been arrested for 5 or 10 minutes, or the arm has been congested by throwing 70 mm. Hg pressure onto the veins for longer periods. In the first case the mottlings are washed out by the hyperæmia, but quickly reappear in their original forms and places ; in the last case they remain unchanged throughout.

There is a condition well known to dermatologists in which mottling on the legs becomes pigmented, usually through the subject sitting, long and often, close up to a fire. Notable examples of this occur on the skin of the shins (Fig. 75, page 263). The bands of pigment overlie and map out exactly areas of skin in which there is a deeper vascular colouration and the pattern of such mottling is identical in all its details with that here described. In some cases it co-exists with unpigmented mottling of the skin of the calves,

and the pigmented pattern of the shin then passes continuously into the fainter and unpigmented pattern of the calf (Lehner and Kenedy *151, 152* and *161*).   The pigmentation is clearly associated with the corresponding dilatation of the underlying minute blood vessels.   It is in this instance impossible to take the view that the red and white areas of mottling change from time to time, otherwise the pigmentation would be diffuse and would not form the reticulated pattern on the skin that is seen.

Speaking of mottling of the skin, whether on the hand or limb, it is perfectly clear that, when simple precautions are taken to maintain the subject and the skin examined under constant conditions, no material changes occur either in the form or in the positions of the red and white areas over periods of hours.   On the contrary the pattern shows considerable stability, and it is only when the skin is submitted to varying conditions of pressure and friction, such as occur inevitably in unguarded skin during periods of many days, that any substantial change is seen ;   even so, with appropriate measures and further observation, the pattern will nearly always revert in general and in detail to its original form.

The behaviour of individual capillaries.

By general consent the capillaries of the nail bed present a picture of considerable constancy from moment to moment and day to day (Hagen *102,* Neumann *199*) ;   it is the rule for all to be open ;   the rate of blood flow alters in these however, and it does not always change simultaneously in neighbouring capillary loops (*52* and personal observations).   In regard to the capillaries on the dorsum of the hand or upon the skin of the forearm, I have been unable to confirm Carrier's conclusions.   In making these observations illumination should be bright and favourably directed, the subject and the skin examined should be at absolute rest and should be so maintained for 15 or 20 minutes before observation begins and during the observations ;   for this reason the observer should not use his own skin.

A complete sketch is made of all the visible capillaries in half a square millimetre of skin, those that are indistinct being included, and thorough familiarity with the field acquired.   The arm examined should be horizontal, so that the veins are undistended, and the room moderately warm (17° to 20°C).   It is the rule to see capillaries of all grades of distinctness down to invisibility and, as the eyes become accustomed to work that imposes much strain on them, more and more vessels are discerned.   It is a most important matter that the positions of as many capillaries as possible should be ascertained and charted at this preliminary examination ;   then in subsequent examinations they are much more quickly and certainly recognised, for attention is now concentrated upon the precise points in the field in which vessels are known to be.   The skin examined is by no means fully transparent,

and a clear view of the vessels is never obtained ; capillaries that lie a little deeper, that are narrow, or that lie in unfavourable planes, are often difficult to identify ; many can be seen only if the utmost attention is given to detail in this work. When the preliminary search is complete, the field is re-examined and the visibility or invisibility, the distinctness or indistinctness, of each capillary previously charted and numbered is noted. It is re-examined repeatedly at intervals of a few minutes. The venous pressure in the arm is now raised artificially, a procedure bringing the capillary tufts into much clearer view, and the vessels are again checked from the chart.

Using this method (*161*) I have examined six subjects fully and many less fully, the skin watched being usually that on the dorsum of the hand ; the results may be stated broadly. The number of capillaries to the square millimetre, counted under severe venous congestion, varied between 39 and 77. During examinations of the same area of skin, preceding venous congestion, the percentage of capillaries remaining invisible, but not necessarily *unopen*, never exceeded 16 per cent. ; it was usually about 12 per cent. The change in the visible capillaries of the uncongested skin over periods varying from 43 to 75 minutes was inappreciable in every case examined.

On rare occasions one or two capillaries that had been distinct became less visible and *vice versa*, or an indistinct capillary seemed to vanish. The most frequent event was the detection of one or two capillaries, previously unseen, an occurrence in three of the six subjects. These capillaries were never more than dimly visible, except when affected by venous congestion and, since they were usually discovered at the 2nd or 3rd examination, and were always detected at subsequent examinations, it is probable that they were at first overlooked because attention was not concentrated sufficiently upon their particular localities. A similar event is the not infrequent detection of capillaries, subsequent to the release of venous congestion, for during the period of congestion their position is accurately noted.

From these observations, it is clearly to be concluded that in skin examined under the natural conditions here named, the majority of the capillaries are open and that their tone is relatively stable and unfluctuating. The statement that the capillaries of the skin are continually opening and closing * is one which I am unable to accept, and sufficient observations seem to me to have been made to justify the conclusion that this is not normally (usually) the case.

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* In point of fact the example given by Carrier (*43*) is unconvincing and does not support the wide conclusions drawn from it. A field known to contain 20 capillaries was under observation, and of these 13 remained invisible while the counts were made, the skin being then unflushed ; that is to say these 13 presented little or no change throughout. The emphasis is laid on the remaining 7 ; of these 1 remained open throughout ; 2 were lost sight of at a single examination ; and the remaining 4 were seen on one occasion only.

Regulation of flow.

The system of irrigation.—The conclusion just stated is intended to apply to the skin, and to that of the human being only.

Hagen (*102*) has observed greater changes in the vessels of the rabbit's ear, in which, however, the tone of the main vessels is well known to vary frequently and greatly. Krogh (*137*) cites his own observations upon the frog's web, in which the changes appear not to be conspicuous, and on the frog's muscle (*134*); Richards and Schmidt (*217*) have noticed an opening and closing of separate capillary loops in the glomerulus of the frog's kidney.*

Krogh (*134, 137*) builds these and Carrier's observations upon the cutaneous capillaries of man into a generalisation. His rendering of the present day conception of the local regulation of capillary flow is that a very small number of open capillaries suffices to supply the resting tissue and that the position of these open capillaries is continuously changing, a cell, starving at one moment, obtains all it wants when the capillary nearest to it is opened up. In this way an adequate, though intermittent, supply can be secured at every single point.

It is not intended to deny that capillaries in other tissues may behave in this manner, but simply to state that human skin should not be included in such a generalisation. In human skin an increase or a decrease of flow is obtained by an increase or by a decrease in the rate of flow through the capillaries as a whole, rather than by the opening of additional or the closing down of redundant capillary channels.

Nutrition is not the sole function of the cutaneous circulation; an important function is dispersion of heat from the body surface, from which point of view the utilisation of many capillary channels rather than a few, presents obvious advantages. Hagen (*103*) describes a periodic change in the size of capillaries of the skin, which is associated with that of the diurnal change of temperature. It is conceivable that because this function of dispersing heat is almost peculiar to skin capillaries, the regulation of their flow is likewise peculiar.

Evidence for local metabolic regulation. The chief evidence that has been brought as yet to show that local metabolism influences blood flow to the corresponding cutaneous territory, consists of the phenomenon reactive hyperæmia, considered in a previous chapter, and the supposed intermittent opening and closing of the capillaries just discussed. This evidence taken as a whole is insufficient; it is defective particularly in failing to demonstrate that an increased flow of blood to the skin causes the vessels to close down. That this is so is shown by the following observations.

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* But they do not believe that these changes are often due, if ever, to the contraction and relaxation of the capillary walls; their detailed evidence calls attention rather to the afferent arterioles and to the points where these divide into capillaries. If local metabolites are the cause of the changes, it would be necessary, seemingly, to assume that their concentration may be very different around the mouths of three separate capillaries that all spring together from the end of a minute arteriole. Such a conception presents almost insuperable difficulty.

When a 1 in 300 histamine solution is punctured into the skin—a strong solution should be used because the consequent flare is more persistent—a widespread flare soon surrounds the site of the needle puncture.   If this flare is watched, it will be found that soon after it comes to its height, it begins to fade in a peculiar manner. It tends to recede first marginally but irregularly, so that at its borders, and subsequently over the greater part of its extent, the area involved is spotty or finely speckled. The point to which attention is now drawn is that the skin that surrounds the flare as a whole, and that intervenes between the spots of the fading flare, is usually distinctly whiter than is unaffected skin (Fig. 24, page 61) ; often these areas are intensely pallid. As the flare recedes, so it is closely followed by the pallid zone, which frequently becomes broader, since its inner edge advances more rapidly than its outer edge retreats ; not uncommonly the whole area that has been flushed by the histamine is universally pale by the time the flare has disappeared ; it may remain so for a long while afterwards. The white areas are seen 2 or 3 minutes after the flare comes to its height.

At first the possibility was considered that they arise simply by blood being diverted from them, the main stream flowing to the flushed zone. This explanation is insufficient, for the pallid areas will persist for a considerable while after the circulation has been arrested to the skin area affected. This observation and the occasional complete replacement of a preceding flare by pallor, place this particular explanation out of court.

Now the histamine flare is due to an arteriolar dilatation consequent upon a local nervous reflex. The capillaries and minute venules, which are also involved, are dilated passively and they are directly responsible for the redness of the skin as we see it ; that the flare is not due to a *direct* action of the poison on the dilated vessels is probably important from our present point of view ; the flare is not due to a local call of the tissue cells, but is a response to a distant stimulus. Thus, the tissue cells in its territory receive, while it prevails, a quantity of blood beyond their needs ; consequently, when the flare subsides, any call that the tissue cells send forth will be for a reduced blood flow. It is to such a call that the blanching is attributed.

The case is different from that of a skin flushed by a more direct stimulus such as moderate heat or friction ; here the dilatation is called forth by a local stimulus, persists while the stimulus lasts, and subsequently leaves no visible pallor.* Thus, pallor tends particularly to follow an increased blood flow to areas of skin that, though they have been flushed, have not themselves needed this increased flow for nutritional purposes.

If the areas discussed are not rendered pale by simple diversion of blood from them, they must be pale because the vessels supplying them have assumed an increased tone. It can be shown that the vessels assuming this

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* Such at all events is usually the case, though heat hyperæmia may also be followed by transient pallor in certain circumstances. If such hyperæmia is called forth by soaking the arm in water at 42°C. and the arm is transferred when reddened to a bath at 34°, a reversal may at times be seen, the skin previously warmed becoming paler than the previously unwarmed skin.

increased tone are those directly responsible for skin colour, namely, the minute vessels. A congesting pressure is thrown upon an arm, the skin of which is already displaying a histamine flare with its circumferential pallor. The flare soon stands out red against a general blue background, but between the two the pallid, sometimes the almost white, zone persists or by contrast is enhanced. Tested in this way the minute vessels of the pale zone are found to withstand venous pressure of as much as 70 or 80 mm. Hg for considerable periods of time. If pressure is exerted momentarily with the finger on the blue skin, the area of pallor produced thus mechanically at once disappears when the finger is withdrawn; the blue colour suffuses into it again from its margins. Pressure readily displaces blood from one area of the superficial venous plexuses to another and, under a congesting pressure, it as readily returns; the anastomoses between these venules are exceedingly free. When, therefore, these venules remain blanched, although the blood is standing under considerable pressure in their turgid neighbours, their blanched condition can be due only to their firm contraction and to their refusal to re-admit blood.

Thus it is shown that the replacement of the flushed by the pallid skin, in the histamine reaction, is due to increased tone in the minute vessels of the skin; it is not passive and the result of arteriolar contraction. The contraction of the minute vessels first becomes effective at the margin of the flare, where the pressure, within those of the minute vessels that are dilated, is presumably lowest. Later it is seen within the main area of flare; it breaks the latter into islets. These islets are considered to represent the central parts of arteriolar territories (see page 43). When the arterioles at first open up to produce the flare, this is confluent but, as the tone of the minute vessels gradually increases, it overpowers the passive effect of the increased stream, and the skin pales, first at the margin of the whole flare, then around the borders of separate arteriolar territories and finally over the whole area.

The increased tone of the minute vessels in response to the increased blood flow may be interpreted in one of two ways. It may be a direct response to increased pressure within them, or it may be, as previously suggested, a response to the nutritional effects of the increased flow. In the case of the histamine flare, while it is possible that both factors are concerned, the second is certainly involved; for, as we have seen, the pale areas persist when the pressure is rendered uniform in the vessels of the arm by arresting the circulation; not only do they persist, but they return if during the arrest they are obliterated by gently pressing on the skin, temporarily blanching it and the surrounding skin.

There are parallel examples of equal interest to that of histamine. I have long observed that skin areas reddened by injury become surrounded by zones of pallor.* Thus, such zones of pallor are usual around

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* The white halo now described is to be distinguished from the brief white reaction described in Chapter II (Fig. 9, page 27). In this the line bordering the red appears early and does not persist.

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any small area of infected skin, and around the local redness that is left often for hours or days after the skin has been punctured with histamine or otherwise irritated, as by flea bites, or after damaging it by freezing or excessive heat. The redness of the skin produced by warmth is a further illustration. If the arm is immersed and held still in water at 42°, and is subsequently immersed more deeply in a tepid bath, the sharp line of redness that demarcates the warmed skin often becomes bordered by a narrow but intense band of pallor. The red erythema produced locally by ultraviolet light usually presents a similar white halo.

From a large number of observations the conclusion is reached that the presence or absence of this circumferential or bordering pallor is governed by one main circumstance, namely, by the state of blood flow through the neighbouring red area ; if blood flow is here increased, the surrounding skin is pale, and the greater the central flow, the more conspicuous is the surrounding pallor. The most sensitive test that we possess to identify this enhanced flow in the central area is congestion of the arm by throwing a pressure of 70 mm. Hg upon its vessels. In 3 minutes the arm becomes cyanosed. Little areas of skin previously reddened by injury of various kinds either remain red, in which case the blood flow through them is known to be increased, or they become blue, as does the rest of the skin. Those that remain red are the ones which were originally encircled by a zone of pallor ; those that become cyanosed are the ones which have presented no surrounding halo. I have seen innumerable examples conforming to this rule and none but rather unconvincing exceptions to it. In the case of areas reddened after they have been frozen, it is usual for these to be surrounded by a pallid zone for a few days ; during this period an increased flow to the damaged skin can be demonstrated, at first by its higher temperature, later by its remaining red when the arm is congested. Later still the pale halo is lost ; then increased flow can no longer be demonstrated centrally. In the macular eruption of measles it is not infrequent to see the red spots surrounded by white rings, and it is to be observed that the brighter the colour of the red spots, the more distinct is the halo. Thus spots freshly erupted show the halo most definitely.

Comparable instances occur in the case of small telangiectases of the skin of the arm and hand (*162*) ; those through which the blood flow is enhanced, according to the same tests, present similar haloes, those in which there is no increased flow do not. This example is important because, while in the instance of injury or of an eruption it may be held that the central area contains an excess of vasodilator substances, which may tend to diffuse outwards, here this cannot be supposed.

Taking these examples as a whole, and in contrast to the histamine flare, they are of consequence because in many of them the pale areas are seen on skin known not to have been flushed with blood, at all events for a long while previously. Here the pallor is more clearly a pure nutritional phenomenon. There is the central area of skin in which the blood flow is

increased, and outside it a pale zone of skin, 1, 2, or exceptionally 3, 4 or 5 mm. of almost uniform width, in which no sign of increased flow can be detected.

The pale zones in each of the instances now described behave as do those surrounding and invading the histamine flare, they are zones in which the minute vessels of the skin are in an active state of contraction.

In parenthesis it may be stated that the white halo encircling an area of redness due to minor injury is in no way controlled by the nerves of the skin. It occurs on skin rendered completely anæsthetic by surgical section and degeneration of its nerves, and on this skin is indistinguishable from the similar halo on control skin of the same subjects (*167*).

I believe that these zones are pale because there is movement of the intracellular fluids from the bordering to the central zone, or that the vasodilator substances natural to the fluid diffuse to, and are picked up by, the outermost vessels that are dilated ; the skin of the pale zone is thus supposed to benefit from the neighbouring enhanced blood flow. In support of this contention there is a simple experiment.

If three or four needle pricks are put down in a line upon a warm skin, the skin soon presents a very faint flare around them for a distance of perhaps a centimetre in every direction. This flare is neither sufficiently intense nor long lasting to bring pallor in its train. About 2 or 3 minutes after the pricking, a red spot is seen to surround each point and, with its development, a white halo also appears about it. The halo develops a breadth of about 1 to $1\frac{1}{2}$ mm.. It persists as long as the central red spot is bright in colour, a matter of very many minutes or hours.

Thus, according to the view expressed, movement of the substances concerned and dissolved in the fluids of the tissue spaces will occur over a distance of 1 to 2 mm. in 2 or 3 minutes. If, instead of using the simple needle prick, we puncture 1 in 300 histamine or 0·1 per cent. adrenalin into the skin, the point of needle entry will become the centre of a red or white spot, respectively. From a number of such observations it has been calculated that the red spot of histamine advances from the puncture by about 1 to $1\frac{1}{2}$ mm. in 1 to 2 minutes ; the adrenalin pallor advances 1 to 3 mm. in 1 to 2 minutes. Thus the rates of movement are not dissimilar to that supposed to occur in more natural circumstances.

Two views of local regulation. The view expressed by Krogh supposes that each capillary forms a unit, through which the blood flows intermittently, and that nutrition of the skin is rendered uniform by continuous diversions of the stream from this capillary to that. As we have seen, this individualistic behaviour is unsupported by recent observation ; likewise it finds little support theoretically.

If within the space of 2 or 3 minutes vasodilator or vasoconstrictor substances are able to move almost an equal number of millimetres, and to influence vascular tone over that range, then it is difficult to believe that the concentration of natural tissue substances at points of the undamaged and

resting skin, separated by no greater distances than those between adjacent capillaries, namely, about a seventh of a millimetre in the skin of the back of the hand, will differ so widely that one capillary will be caused to dilate and its neighbour to contract to obliteration, thus to be maintained for periods of several minutes.

It has lately become the custom, in speaking of the physiology of the smallest vessels of the skin, to restrict the term capillaries strictly to the anatomical capillaries, and this custom I have here followed. But there has been an unfortunate tendency to overemphasise this distinction between capillaries on the one hand and the minute venules and terminal arterioles on the other. They are all simple endothelial tubes and together constitute a meshwork of vessels, which we have every reason to believe acts harmoniously and to common purposes. Although this meshwork, from a strictly anatomical standpoint, is separable into constituent parts, yet physiologically it has not been so subdivided. Agencies which act on the one part—and this has been ascertained, as earlier chapters illustrate, in many directions—act in a similar way upon the remaining parts. When the opening and closing of individual capillaries in the skin is spoken of, small and particular elements are picked out of a complex system and are given undue prominence ; and by so particularising we are led away from the more correct conception of minute vessels acting together as a physiological unit.

It is not to be assumed that interchange between blood and tissue spaces is confined to the capillary wall ; it almost certainly occurs also through the walls of the terminal arterioles and minute venules. Functionally these vessels are to be regarded as belonging to the capillary system. The gaps between adjacent capillaries are frequently filled by vessels of these orders, though it is true that they lie slightly deeper in the skin than the capillaries themselves. The anatomical capillaries are confined, according to Spalteholtz (*231*), to the most superficial strata of the skin ; nutrition of the epidermis must occur by diffusion from these, and nutrition of the deeper layers of the skin probably by diffusion, or by movement of fluids, from the endothelial walled vessels as a whole. Diffusion and a movement of fluids are obviously important in promoting uniformity.

In considering the effect of local metabolism on these minute vessels, it is quite possible to conceive that minor and independent changes of calibre occur in its individual constituents in response to slight differences in the concentration of substances in the surrounding tissue spaces ; but such changes can scarcely be of any great functional importance. Conspicuous changes of calibre can hardly occur, for the reasons given, except over relatively wide areas of the meshwork. My own conception of the local regulation of blood supply to the skin is a regulation in the flow through the *meshwork of minute vessels.* Here we are upon much safer ground, distinct evidence having been brought forward that local metabolism affects tone in this meshwork.

There is also, as has been described, a balancing action between the minute vessels on the one hand and the strong arterioles on the other. When the arterioles open up, the flow to the skin is increased ; but, if the flow is in excess of the needs of the tissue, as it will be when the arteriolar dilatation is forced at a distance from the point of stimulation, then the appropriate group of minute vessels will shortly assume increased tone in the territory in which the nutritional balance is upset, and will help to restore this balance ; at the same time a greater flow to the area requiring it will be ensured.

General comment.

It has been shown that the blood flow to the skin is affected locally in deliberate injuries of very varying kind by the liberation of a vasodilator substance, dilating the vessels with which it comes in contact and, through a local nervous reflex, the arterioles at a distance. Evidence has been brought forward to support the conclusion that a local release of a vaso-dilator body is also responsible for the redness of the skin produced by moderate heat, and for that following when the circulation to the skin, having been obstructed, is released. In both the last named instances, as discussed in the appropriate places, the facts clearly point to the possibility that the vasodilator body is a normal metabolite. The evidence that is given in the present chapter is of particular value, because it is perhaps the most direct we possess that when blood flows to tissues in quantities in excess of their needs, the minute vessels, by a purely local and non-nervous mechanism respond and check the flow.

If we consider this demonstration in conjunction with the effects of brief obstruction of the circulation, an interference that relaxes the minute vessels and produces reactive hyperæmia at the release, then the conclusion becomes legitimate that the balancing mechanism described is reversible, and therefore complete from the functional standpoint ; it is a mechanism that opens the minute vessels when the tissues are undernourished and closes them when they are overnourished. So much must I think be accepted.

CHAPTER XIV.

REGULATION OF BLOOD FLOW BY CENTRAL NERVOUS CHANNELS.

Introductory.

In mammals physiologists recognise vasomotor nerves of two orders; stimulation of the distal ends of these nerves produces vasoconstriction and vasodilatation, respectively.

The vasoconstrictor nerves are all sympathetic; they pass as medullated nerves from the spinal cord to join this system exclusively through the white rami communicantes of the thoracico-lumbar region. Passing to the body walls, limbs and head and neck, they form synapses in the distinct sympathetic chain ganglia and in the combined ganglia of the same chain in the cervical region; here are their cell stations. From the sympathetic cells the vasoconstrictor fibres to the body walls and limbs return unmedullated through the grey rami and join the segmental spinal nerves, the trunks and branches of which they then accompany until they are distributed to the walls of the blood vessels.

From the somatic nerves, sympathetic fibres pass as early outgoing branches to the main vessels, while later and later offshoots run their courses to the vessels as these in branching become smaller peripherally. The sympathetic fibres, when they reach the vessels, form intricate plexuses in their adventitial walls, from which plexuses fine fibres, which also become enmeshed, run into the media (*270*). The adventitial plexus, while continuous, is frequently reinforced by other incoming fibres of the same class.

The vasoconstrictor nerves exert a tonic influence on the vessels. General vasoconstriction results reflexly when the central ends of sensory nerves, such as the sciatic, are stimulated.*

Our knowledge of vasodilator nerves is less precise. The *chorda tympani* and the *nervi erigentes* of the pelvis are the most familiar examples; these when stimulated distally induce flushing in the organs they supply; in the first

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* This action is in part indirect, as Anrep has shown, and is due to the release of adrenalin from the suprarenal glands (*4*).

case, however, the action has been thought by Barcroft and Kato and Piper (*5, 6*) to be exerted indirectly through an increased metabolism of the submaxillary gland, a possibility still debated (*15*). Evidence pointing to the existence of vasodilator fibres running in the sympathetic chain has been brought forward in a few instances ; thus Dale (*53*) paralysed the vasoconstrictor fibres by means of ergotoxin and subsequently obtained flushing of the skin of the cat's foot by stimulating the abdominal sympathetic.

General vasodilatation may be produced reflexly, notably by stimulation of the depressor nerve.

In certain instances it has been shown that appropriate local vasodilatation follows reflexly when a sensory nerve is stimulated centrally. Thus, the rabbit's ear flushes when the central end of the posterior auricular nerve of the same side is stimulated. These relatively localised reactions are referred to as the reflexes of Lovén, who first described them (*180*). According to Bayliss (*15*) the Lovén reflex takes place in part through vasodilator nerves and in part by the inhibition of vasoconstrictor impulses ; he believes in a similar double action where the general depressor reflex is concerned.

This brief outline of the paths through which blood vessels, including cutaneous vessels, are controlled by the central nervous system, will serve to introduce problems that especially concern, and evidence that is derived from, the human skin. One chief omission, namely, antidromic innervation, will be considered separately a little later.

Vasomotor effects in the skin.

Influence of cervical sympathetic ; *emotional blushing.* Since Claude Bernard's time it has been known that the cutaneous blood vessels of the head and neck are supplied by vasoconstrictor fibres through the cervical sympathetic. Peripheral stimulation of this nervous cord blanches the skin, section of the nerve flushes it. Surgical section of the cervical sympathetic in man flushes and warms the skin of the face on the corresponding side, contracts the pupil and narrows the palpebral fissure, as in the uncomplicated instances described by Kohler and Weth (*130*) and by Levine and Newton (*156*).

This group of effects is sometimes seen in cases presenting tumours of the mediastinum, more especially aneurysmal tumours ; and in this instance they are generally attributed to paralysis or paresis of the sympathetic nerve supply as a result of pressure upon the nerves in the thorax.*

When the face is red and warm in these cases, the whole facial skin of the affected side appears to be involved. An example of the kind, in which

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* Inequality of the pupils in cases of aneurysm, however, is said also to result from unequal blood supply to the two sides of the head (*258*).

readings from the skin relate the temperature in different parts, is given later on page 269 of this book. I am unable to say precisely how far the vascular dilatation or heat spreads down the neck, or what effect the lesion may exert upon local or emotional reactions of the vessels of the facial skin. Vascular effects of lesions of the kind described have received less detailed study in man than they deserve. It is known that the visible flush may persist for very many months and that in other instances it quickly subsides.

The mechanism involved in emotional blushing is not known with certainty ; the visible area involved is usually confined to the head and neck ; this is the chief ground for ascribing the blush to inhibition of cervical sympathetic fibres.* It is not infrequent to see the blush spread farther, so that it involves a lesser or greater area of the chest and back ; here it would be necessary to assume that other nerves are brought into play.

A matter of interest is the usual confinement of the blush to the face ; here also it comes most brightly ; this is discussed later and at length on page 257.

Interruption of other vasomotor tracts. If a nerve such as the sciatic is cut in the cat or dog, the temperature of the corresponding skin soon rises, the skin becomes red, and the arteries to the limb pulsate vigorously, according to Goltz and others (*59, 98, 141*) ; these effects are due to interruption of the vasoconstrictor fibres to the vessels of the limb, † for similar phenomena follow when the corresponding sympathetic ganglia are removed. They do not persist indefinitely. Goltz (*98*) stated that when the nerves to a dog's leg have been cut, the higher temperature of the affected foot begins to fall away in a few days and equals that of the unaffected foot in a few weeks.‡ Dale and Richards state that flushing of the cat's foot, following section of the sciatic and anterior crural nerves, passes off rapidly, even during the actual period of the short operation (*59*).

Effects similar to these are seen in man. Thus Trotter and Davies (*252*) cut the nerves to cutaneous areas in their own limbs and describe a flushing of, and rise of temperature in, the skin ; the redness seen by them was unpronounced though distinct, and corresponded to the anæsthetic area very closely. These signs diminished in a few days and vanished in a few weeks. They found that section of the great auricular nerve in man produced bright flushing, confined to the ear and lasting a few days.

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* Flushing has been ascribed sometimes, according to Krogh (*137, page 45*) to the antidromic impulses that are presently described ; but he says it is improbable that the sensory nerve channels are involved, since removal of the sensory part of the trigeminal nerve in man does not affect the emotional reaction of the vessels ; Professor Krogh writes to me that he has relied upon the statements of surgical colleagues in this instance. Davies (*61*) states that he found no vasomotor anomalies of the facial skin in the large series of cases of extirpation of the Gasserian ganglion that he examined and watched, and Kraus (*133*) makes the same statement ; but it is not specifically stated by either worker that the emotional blush occurs.

† In part perhaps to irritation of nerve fibres which Goltz regarded as vasodilator (*98*).

‡ Subsequent effects, the part becoming cooler and often reddened or otherwise discoloured, I do not discuss, since they largely result, when present, from disuse.

Nerves running to the skin, or the main nerves of the arm, may be blocked by injecting a local anæsthetic ; working on the former, Grant and I (*164*) saw a faint flush over the area rendered anæsthetic ; this lasted 10 to 15 minutes, when the skin resumed precisely the colour and temperature of that surrounding. Working similarly on the latter, Breslauer (*28*) saw no flushing, but Wiedhoff (*265*) observed reddening, increased pulsation, and a conspicuous rise of temperature. In cases where cutaneous nerves of the lower abdomen and thigh have been cut surgically, the skin if unmolested presents a normal colour a few weeks after operation ; in some instances a slight increase of temperature ($\frac{1}{2}$°C or less) is found, in others there is none (*167*).

Sufficient has been said to show that the effects produced by lesions of peripheral nerves are substantially the same in man and lower animals. That these vasomotor tracts are sympathetic is indicated by Kohler and Weth's observations (*130*). They examined very thoroughly a patient, in whom the cervical sympathetic chain had been excised : the lower pole of the superior cervical ganglion and the whole nerve and lower cervical ganglia were removed, down to the level of that on the 1st dorsal nerve. The skin of face, neck, and arm on the same side became brightly flushed and hot ; the flush, in the arm at least, soon began to subside and had disappeared within a few weeks.*

The recovery of vascular tone in skin that has been flushed remains insufficiently explained. In the instance of Dale and Richard's cats (*59*) recovery of colour long preceded that of temperature, the skin of the foot becoming pale while remaining hot ; and this state continued for at least 2 months. These workers attribute the recovery of colour in this instance to greater tone of the minute vessels, the continued warmth to persistence of arteriolar dilatation, an explanation fully in accord with their observations. I suggest that the quick and persistent increase of minute vessel tone, seen by them, is in part a balancing effect such as has been described on page 200, and due to the exaggerated blood flow through the foot ; a similar reaction may explain the pallor that Burgess describes as sometimes quickly succeeding blushing of the human face (*36*). Differences in the vigour of the endothelial vessels in different species of animal may account, in part, for variations in the visible skin reaction to nerve injury and in the time of apparent recovery. It may be that an unusual vigour of these vessels in the skin of the human trunk and limbs accounts for the relative faintness of the flush that usually follows nerve injury. The only part of the human skin that habitually reddens greatly when deprived of the appropriate nerves seems to be the facial skin ; as will be seen subsequently, the vigour with which the corresponding

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* The cat's forepaw after reddening becomes pale usually within a few days of removal of the stellate ganglion, though remaining warm or becoming warmer. The nostril of the same side becomes reddened and remains so, at least for weeks ; it is to be remembered that the operation leaves the superior cervical ganglion intact ; pallor is not uncommon when this ganglion is removed and the nerves are allowed to degenerate (*173*).

minute vessels contract is in general much less than in other cutaneous regions.

Vasomotor reflexes in the arms.   The effects of heat and cold upon the human limbs are in part reflex.   These reflexes and their contribution to the change in skin colour have been discussed in Chapter X.   They affect not only the same but also the opposite limb ; the efferent path is sympathetic and in the main nerves of the limb.   Thus, in the hand, anæsthetisation of its nerves on the unstimulated side abolishes the reflex (Wiedhoff, *265*), as does removal of the lower cervical sympathetic ganglia (*130*).   Painful stimuli applied to the skin exert a constrictor influence in the opposite limb through similar reflex channels (*265*).   It does not seem to be known definitely whether the reflexes here described are merely part and parcel of a general vaso-constrictor reflex, or whether in some instances (as in the heat reflex) they may not be more closely allied to Lovén reflexes.

Periarterial dissections.   This subject will be dealt with only briefly as it is still largely controversial.   Leriche (*154*) has stated in recent years that, if the adventitial coat is stripped from a length of the main artery to a limb in man, vasodilatation of this limb sets in.   His statement has been confirmed by other surgeons (Brüning and Stahl *33, 34*), and the operation has been widely used, and apparently with success, to relieve vasomotor disturbances in the limbs, more especially those associated with pain.   The vasodilatation is evinced by flushing, a rise of temperature and increase of pulse volume, and this condition is stated to persist for variable times, from a few days to several months.*   It has been explained in different ways.

The original suggestion that it is due to the division of vasoconstrictor fibres running in the adventitia of the arteries, appears to be untenable.   Observers are agreed that both in animals and in man the efferent vasomotor fibres pass to the arterioles exclusively through the peripheral nerves, because they are unable to obtain any of the known vasomotor effects by central or reflex stimulation, after these nerves are divided or anæsthetised, and because they can obtain these effects after dissecting away the adventitia of the main vessel (*90, 145, 224, 265*).   It seems clear, therefore, that, although the nervous plexuses on the arteries and arterioles are continuous, they do not serve to convey efferent impulses for an appreciable distance.

An alternative explanation, which has gained a good deal of support, is that there are afferent (sensory) paths on the main blood vessels, and that these are concerned in reflexly determining the tone of the vessels in the limbs (*34, 90, 113, 150, 224*, see, however, *63*).

Very full references to the questions here briefly discussed will be found in several recent articles (*38, 149*).

Antidromic sensory paths.

It was found by Stricker (*240*), and the fact has been amply confirmed by Bayliss (*12*) and by Langley (*143*), that the skin of the limbs flushes when the cut posterior roots of the spinal nerves are stimulated peripherally.   The reaction fails if the peripheral sensory nerves have previously been cut (*143*), but a similar reaction of the skin is seen if these nerves are excited distally (*12, 82, 144*) ; the fibres here concerned belong to the posterior root system, degenerating when the root ganglia are removed but not when the roots are cut between spinal cord and ganglia (Bayliss *12*).   The last authority regarded this system as forming the sole supply of vasodilator nerves to the

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* It is not altogether clear to what extent these evidences of increased flow may not be due to the incision, manipulation and subsequent bandaging of the corresponding limb ; though the lasting after-effects described can scarcely be explained in this way (see Lehman, *149*).

limbs (*15, page 31*). The impulses in these experiments are thus shown to be carried by the sensory nerves antidromically, and ultimately, so it has been supposed, to reach the vessel through sensory nerve offshoots.

According to the observations of Woollard (*270*) the plexuses found on the arteries are of two kinds, non-medullated (sympathetic) and medullated (sensory). The latter chiefly participate in innervating the smaller arteries and arterioles. When traced peripherally the sensory fibres are seen to throw off collaterals ; these end in special terminations in the adventitial walls of the arterioles, in the surrounding fatty connective tissue, in Pacinian bodies, and presumably also in nerve endings to the skin.

The experimental results described are unquestionable, yet they do not prove that natural impulses are conveyed from the central nervous system along these channels to the vessels, and the physiological significance of antidromic conduction has as a consequence remained obscure. The difficulty of regarding the antidromic impulse as comparable to that conducted by vaso-motor nerves in general has been realised by several physiologists. Thus, in Bayliss's paper (*12*) the idea that they may liberate metabolites is mentioned, as it also is by Langley (*144*), who appears to have made the suggestion originally. Gaskell (*92, page 97*) also refers to the possibility of acid meta-bolites being released. But in none of these writings is there any evidence for such a mechanism, which, therefore, has so far remained inacceptable.

I have been brought independently to consider a similar working hypothesis and by the following train of thought. Whenever a sharply circumscribed reddening of the skin, standing by itself or associated with the appearance of a central wheal or blister, has been observed, experience has forced the preliminary assumption that this reaction is the result of H-substance released in the skin so affected. The assumption, whenever it has been possible to put it to the test, has been consistent with the results of such tests. One phenomenon, however, still remained and, being unexplained, stood in the way of the full generalisation that has been stated on page 91 ; this phenomenon was herpes zoster.

Herpes zoster is a skin reaction of the class considered, yet it is correlated, not with local injury, but with a lesion in the posterior root ganglion. Might we suppose antidromic impulses to be capable of releasing H-substance in the skin and to be responsible in man for herpes zoster ? To consider this very evident possibility was justifiable, to formulate the corresponding conclusion, tempting as it might be, would have been unjustifiable, while no directly supporting evidence could be put forward.

But being sufficiently impressed by the idea, and by the importance of bringing it to a decisive issue, Marvin and I (*172, 173*) have set out to obtain evidence one way or the other. We have chosen for the purpose the cat's paw, the preparation described by Langley (*144*). We use the forepaw and stimulate the peripheral ends of branches of the median nerve. This nerve is rid of sympathetic fibres to the blood vessels and sweat glands by excising

the stellate ganglion three or more weeks previously. We then deal with a nerve composed solely of sensory fibres, the sympathetic elements having degenerated. Peripheral stimulation of such a nerve twig produces the usual antidromic vasodilatation in the pads of the feet that the twig supplies. We soon remarked upon several significant phenomena.

Firstly, that short faradic stimulation produces a very long lasting flush of the pad. On turning back to previous records of similar observations we found evidence of the same kind, though its importance does not appear to have been grasped. When vasoconstrictor nerves are stimulated, the corresponding vascular reaction comes quickly and subsides relatively abruptly soon after stimulation ceases. In contrast with this we here find a form of vasodilatation, gradually increasing to a maximal point over a period of about 20 to 40 seconds of stimulation, holding at this point, and then declining over a period of 5 or 10 minutes at an imperceptible rate. The gradual appearance of the flush suggests a cumulative process ; the very gradual decline is strongly reminiscent of the fading of the local reddening to stroking, or of a reactive hyperæmia, and thus suggests the gradual removal of a similar vasodilator body.

Secondly, we noticed that the duration of the response is often clearly related to the duration of stimulation ; that is so at all events in most instances, providing stimulation is not too long. Such a relation is again compatible with the idea of the accumulation of vasodilator substances in the skin.

We proceeded to employ a crucial test, namely, that used in dealing with reddening of the human skin in response to various forms of stimulation and described on page 86. It consists in seeing if the vasodilatation is held up by arresting the circulation to the limb. This is quite definitely the case. If the nerve is stimulated, for say 20 seconds, immediately after such an arrest, and the circulation remains obstructed for a period equal to or surpassing that during which the reaction would otherwise subside (5 to 10 minutes), and the blood flow is then released, all the pads of the feet become brightly suffused. When this reactive hyperæmia passes away, as it does in a few minutes, those pads remain red that have been affected long before by the antidromic impulses, and this redness fades away very gradually. The duration of fading, *measured from the release of the circulation*, corresponds, usually with remarkable exactitude, to the duration of fading, measured from the end of stimulation, in an instance where the circulation has been left unimpeded throughout. It corresponds also, and this is the more perfect control, with the duration of fading when stimulation has coincided with the end of a similar period of circulatory arrest.

If, instead of so testing antidromic vasodilatation, we similarly test the vasodilatation produced by stimulating the nervi erigentes, or the vasoconstriction of the ear produced by stimulating the cervical sympathetic, the phenomenon described does not occur. In these instances the vascular

reaction comes and goes in the same period of time, whether the circulation to the vessels affected is free or arrested. Thus, the contrast is sharp.*

These observations are compatible with one interpretation only, namely, that the antidromic impulse liberates a vasodilator substance in the skin during circulatory arrest, that it is held there until the release, and that it is then gradually removed. We conclude that the antidromic nerve impulse influences metabolism in the cells of the skin, releasing in the tissue spaces a vasodilator substance, and we have in mind especially the epidermis, which, as Ranvier has shown, is plentifully and intimately supplied by nerve fibrils belonging to the sensory nerve system.

We return to the point from which we started and proceed to consider herpes zoster itself.

Herpes zoster. This eruption is preceded and accompanied by severe pain, and comprises reddening and swelling of the skin over a sharply defined area, corresponding to the distribution of a sensory nerve root. The swelling usually progresses, though not universally, to the formation of blisters.

Head and Campbell (*111*), by their well known clinical work, have shown that in herpes zoster the ganglion on the posterior root of the sensory nerves is the seat of an acute inflammatory and hæmorrhagic process ; this essential lesion destroys cells in the ganglion and leads to degeneration in the corresponding posterior roots and peripheral nerves. They believe the eruption, as this is usually seen, to be the display of an acute specific malady, the poison acting selectively.

Identical skin lesions however, may also follow the invasion of the posterior root ganglia by malignant disease, or their involvement by injuries, such as gunshot wounds, as Head and Campbell (*111*), Elliott (*80*) and Morton (*194*) have shown. In a general account of herpes zoster, Head (*110*) remarks upon its occurrence in tabes dorsalis ; he has seen five such cases, and the eruption was situated in every case in the territory previously occupied by intense lightning pains. In Dubler's case of tuberculous necrosis of the ribs (*69*), the ganglia are stated to have escaped, but an intense inflammatory neuritis of an intercostal nerve was found.

Blisters or ulcers are known frequently to follow injuries of peripheral sensory nerves and such lesions have long been called *trophic*. The skin being deprived of sensation, these lesions are often traced to direct injuries, to which insensitive skin is naturally extremely prone ; the exclusion of such unfelt injury is in most cases impossible. This consideration has led to the lesions of insensitive skin being ascribed, too generally, to accidental causes, and has been responsible for much disbelief in the intervention of a " trophic " factor.

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* The real vasomotor nerve very possibly produces its effects through peripheral chemical changes, but, if this is so, these chemical changes are either reversible or the substance liberated is quickly destroyed *in situ*.

The significant cases are not those that display insensitive skin, but those that display hypersensitive skin and burning pain (*causalgia*) after sensory nerve lesions.   This type, outlined by Paget (*202*), and fully described by Weir Mitchell and his associates (*191*), has received less attention than it merits.   It is the case in which a nerve, though not transected, is damaged and is subsequently caught up in scar tissue.   The limb so affected is guarded by the patient with the utmost precaution, not only from injuries, but from contacts of any kind.   The affected skin presents a characteristic picture, it is glossy, red, unwrinkled and hairless, is acutely sensitive and painful, and, so Mitchell states, is almost always the seat of herpetiform eruptions, single or repeated.   The tendency to display herpetiform eruptions may not be as great as Mitchell believed it to be, but that it occurs is borne out by other reports such as that of Charcot (*46*).   Head and Sherren (*112*) have drawn attention to and have illustrated this type in recent years.

To sum up, herpetic or herpetiform eruptions occur as sequels to lesions of the sensory nerve tracts ; not only do they follow irritative lesions of the ganglia, but they are produced also by lesions of those tracts distal to the ganglia themselves.   These lesions are irritative, as is evidenced by the severe pain that accompanies them.

Possessing evidence as we now do that irritation of the sensory nerve system releases antidromically a vasodilator substance in the skin, and realising that herpes results from irritative lesions of the same tracts, we are in a position to conclude that herpes zoster results from release of the same substance.   Herpes zoster shows itself first of all as a reddening of the skin ; this reddening develops slowly and becomes associated with œdema, in the form of simple swelling and local blistering ; thus it falls into line almost precisely with the response to ultraviolet light.   Although the artificial and distal stimulation of pure sensory nerves in mammals has not as yet been shown to occasion œdema, there can be little or no doubt that the released substance is one and the same in both circumstances, or that we have to deal in both instances with what I have termed the H-substance.

This statement is of much importance to my general theory that the H-substance is a normal metabolite, for evidence has now been obtained that it may be released through physiological channels and in sufficient quantity, or over a sufficient period of time, to produce destructive lesions in the skin.

The appearance of blisters in this example of a slow release of metabolites is also of interest in that it substantiates the view previously discussed, that blistering and whealing are not produced through fundamentally different mechanisms.

Reddening and vesication of the skin by suggestion.   Upon statements that local reddening or vesication of the skin can be produced in certain hypnotised subjects purely by suggestion, comment must be brief.   I have read a number of the reports, including that by Jendrassik(*123*) and by Kraft-Ebing (*132*) upon the famous Ilma S., and the strangely identical reports of Bernheim (*19*) and of Beaunis (*17*), two of the eye witnesses of Focachon's much quoted experiments.

The full claim is that blisters can be raised by suggestion on a stipulated area of skin and in a precisely stipulated form and time.

Less unlikely claims have been put forward in other instances, for example when Dumontpallier (74) believed he had produced reddening or warming of the skin by similar means.

These reports, however, seem to me to fail in substantiating the conclusions derived from them. Since subjects, open to the suspicion of deceit, or known to be adepts in deceiving, were under observation, continuous supervision and the employment of suitable controls are often, if not usually, conspicuous by their neglect.

Kohnstamm's observations (131) and the results of Forel published by Moll (193) are weightier and I am indebted to Dr. Maurice B. Wright for relating to me some unpublished observations of his own of a most suggestive kind. In this category must be included also the remarkable observations published by Hadfield (*Lancet, 1917, ii, 678, and 1920, ii, 68*).

It would not be justifiable to deny the existence of some of the extraordinary phenomena described, especially since the antidromic path seemingly provides a channel through which the appropriate impulses may pass from brain to skin ; neither would it be wise to admit the conclusion that local reddening and vesication can result purely from suggestion, without unusually strong, clear and abundant evidence. It can hardly be said that as yet such a body of evidence exists.

CHAPTER XV.

REGULATION OF BLOOD FLOW BY LOCAL NERVOUS

CHANNELS; AND CAPILLARY INNERVATION.

In an earlier chapter I have dealt with a local nervous mechanism in the skin, a mechanism that depends upon the "axon reflex." This reflex will now be considered in more detail, and the relation of the paths taken by the corresponding impulse and those of the antidromic impulse will be discussed.

The local, so-called " axon reflex."

The local or axon reflex has been illustrated fully in this book. The paths travelled are generally regarded as at least in part sensory. It is unobtainable from any part of the skin to which the sensory nerves have degenerated, and the borders of insensitive skin correspond with precision to the borders of the area over which the reaction fails. Moreover, if the stimulus is applied just outside the insensitive area, the reflex flare appears, but will not invade the insensitive skin, the border of which is thus mapped out (*167*). The idea that the sensory nerve endings receive the impulse has grown from this knowledge and also from the fact that any form of stimulus known to produce painful sensations will also elicit the reflex. The last point, however, should not now be used in argument ; for there are forms of stimulation that will evoke the flare without awakening local sensation of any kind (weak galvanic stimulation, chemical irritants such as mustard gas).

Although the reflex appears to start in the sensory nerve endings, the stimulus applied does not excite these directly, but through the release of H-substance *at the point stimulated.*

It is now agreed that the afferent path is sensory and it has usually been thought that the efferent channel begins as a collateral branch of a fibre of the same system. The latter follows because the reflex is known to be purely local and to be in no way connected with the central nervous system, a matter fully discussed in Chapter V. Two views have been expressed as to its terminal path, Bruce (*32*) holding that it is conveyed by sensory nerve channels throughout, Bardy (*9*) believing that the sensory collateral forms

a synapse around a local ganglion cell of the sympathetic system.* The latter view has received no support and, in the case of skin, it would be inconsistent with the general belief that no such cells are placed peripherally; further, unless we were to assume that the sympathetic channel is always short, this view would be placed out of court by the observation that the flare cannot be caused to invade an area of sensory denervation from skin lying immediately outside it. The most conclusive evidence for a purely sensory path is to be found in Kohler and Weth's observations in man; these show that the reflex remains undisturbed after the sympathetic supply to the limb has been destroyed by ablation of the corresponding sympathetic ganglia and after sufficient time for degeneration has elapsed (*130*).†
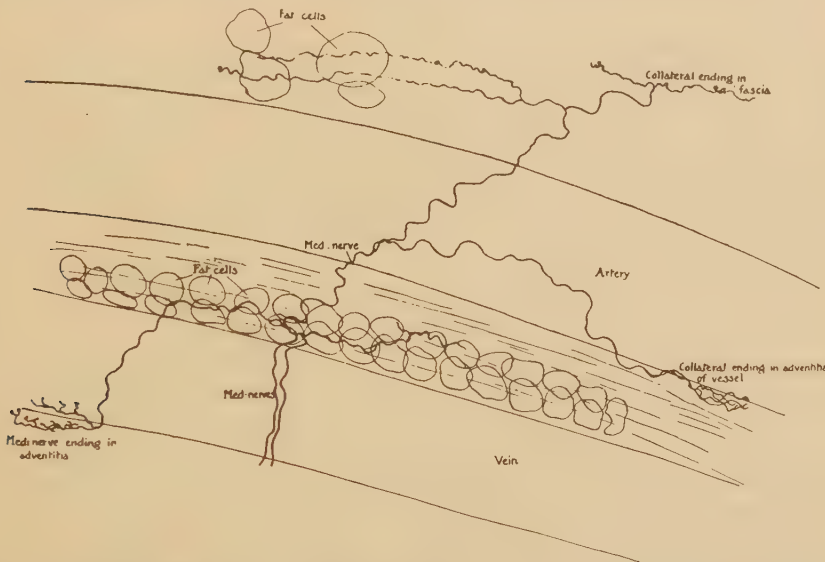
Fig. 63. (× 90) After Woollard. A small artery and vein from a cat, showing the widespread distribution of a sensory medullated fibre. It breaks into collaterals that supply a nerve ending to the adventitia of the artery, and that terminate in fascia and around fat cells.

A clear description by Woollard (*270*) of the collateral branches of sensory fibres, which shows that one and the same fibre may by division supply the arteriolar wall and special sensory nerve endings, provides an anatomical basis for a purely sensory axon reflex. Woollard has followed these collateral paths for a distance of an inch; this is important because, to explain the local reflex, paths of at least this length are requisite. Collaterals of greater length than an inch would be most difficult to demonstrate anatomically.

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* A mechanism more closely resembling that described by Langley and Anderson (*146*) to explain a peculiar reflex through the hypogastric nerves; similar reflexes in preganglionic fibres to the sympathetic chain were subsequently postulated by Langley (*142*) and termed "axon reflexes," the first use of the term.

† Dr. J. C. Fox, of New Haven, has kindly communicated to me some unpublished observations fully confirming this statement.

The extent of the local reflex. If we use histamine as our stimulus, the visible flare spreads over a wider area as stronger solutions are used ; not proportionately to the strength however, but peculiarly. A 1 in 30,000 strength pricked in may yield a small flare, a 1 in 3,000 strength may yield one that is a good deal more extensive, a 1 in 300 strength may cause an even greater surface to redden, but at this point of increasing concentration, or earlier in other instances, a limit is seemingly reached and is not surpassed however much the concentration is raised.

There is, too, this peculiarity ; when seemingly the full extent of flare has been reached, this flare may be awakened in its every detail by later punctures of the substance at the original point. If a flare with its outlying

Fig. 64.   Fig. 65.
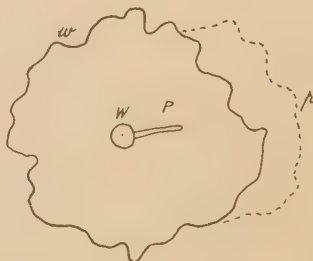
Fig. 64 (× ⅔) Histamine (1 in 300) was punctured into the skin of the forearm at *A* and yielded the flare outlined by the continuous line *a*. The same spot was repunctured 3 hours later with a 1 in 30 solution with a precise repetition of the flare. Two hours later point *B* was punctured with a 1 in 30 solution ; the flare appeared over the area outlined by the dotted line *b*. Several hours later the intermediate point *C* was tested similarly. The resultant flare precisely filled the outline *a*.

Fig. 65. (× ⅔) Histamine (1 in 30) was punctured into the point *W* on the forearm, whealed the skin and produced the flare outlined by *w*. After 4 minutes the wheal began to show a lymphatic extension which lengthened gradually. When it had lengthened to about 1 centimetre, a new area of flare *p* appeared abruptly.

islets, when these are present, is accurately marked out on the skin, repuncture at the same point, later on this or succeeding days, will flush the skin precisely to the old outlines. If the stimulus is moved a suitable distance, usually one centimetre from the first, it is the rule to find that the new flare has likewise moved its borders ; it invades a new strip of skin, and leaves uninvaded an old area of approximately the same size, while the central part of the flare maintains its original outline. The accompanying diagram (Fig. 64) illustrates and amplifies these observations. Puncture at *A* yields flare *a*, puncture at *B* yields flare *b*, and these recur regularly to the appropriate punctures. If we now puncture at the intermediate point *C* one only of two events happens ; the flare spreads over one or other of the original areas precisely.

Similarly, if a strong solution (1 in 300 or 1 in 30) has been punctured in at a single point, an extensive flare will develop and may be outlined. Often a pseudopodic process will later be seen to protrude from the developing wheal (as in Fig. 65) and gradually to extend. This is due to the passage of histamine in adequate strength along a lymphatic channel. While the pseudopodic process extends, the flare remains unchanged in contour, until the narrow promontory has travelled half a centimetre or more; then a new band of skin flares up abruptly beyond the old on the side to which

Fig. 66.   Fig. 67.

Fig. 66 ($\times \frac{2}{3}$). On a strongly mottled arm, several of the paler areas were outlined (continuous lines). Histamine (1 in 300) was now punctured in at A. A diffuse surrounding flare (a) and two small outlying areas of flare (a^1) appeared. To the right, the border of the main flare was strictly limited by the borders of two pale areas (broken line); the remaining pale areas shown became flushed.

Fig. 67 ($\times \frac{2}{3}$). On a less conspicuously mottled arm, the paler areas were first outlined over a wider area of skin and histamine (1 in 300) punctured in at point B. The flare appeared over a very wide area of skin, outlined by the broken line (b). A number of the pale areas (at b^1) failed to flush, the flare spreading between them. In other regions the margin of the flare was restricted by pale areas.

the pseudopodic promontory points (Fig. 65). The two observations are similar and they naturally suggest that, as the histamine moves or is moved by puncture laterally, a new nerve twig becomes involved. This assumption, promising as it seemed to me at first, has proved false.

The step extension of the flare is due to a wholly different cause, namely, to local differences in the tone of minute vessels in adjacent and defined areas of the skin. These areas of varying tone correspond to the mottling of the skin previously discussed and fully considered in Chapter XIX. When the flare reaches a redder area of deficient tone, it spreads through the whole

of it almost without fail ; its final boundary consequently coincides with the proximal boundary of a pale area, where tone is high (Fig. 66). This fact is very readily demonstrable in skins that present conspicuous mottling, and in these the flare, having invaded the whole of one red area, may spring across a paler area without affecting it, to appear in and invade completely the next red area (Fig. 67). In skin in which mottling is less in evidence the last mode of spread does not occur ; nevertheless the flare, as has been said, is limited in its spread by the originally slightly paler contours.

I have found it practicable, in pursuing this subject, to guess and to define with considerable, often minute, accuracy the borders to which the flare of histamine will reach *before that substance is introduced into the skin* ; and this in skins coloured so uniformly that they would not ordinarily be spoken of as mottled. There are in fact few forearms upon which inspection will not reveal very slight mottlings of colour ; these will in greater or lesser measure control the extent of the flare when this appears.

Thus, the extent of the flare when full is controlled in large part by the state of minute vessel tone, and it is for this reason that the radius of visible redness is quite unreliable as a measure of the maximal distance at which the local nerve reflex can act. If on the tested skin there are areas in which minute vessel tone has been weakened many days or weeks before, as by ultraviolet light or by other injury, it is not very unusual to see these areas light up when the histamine flare comes, although the main flare lies some distance away. One of the most striking instances of this phenomenon that I have witnessed was in the case of an old " Lewisite " burn, which Major W. R. Galwey kindly showed me on his own arm. He had himself previously observed that this would light up when the skin was restimulated at a distance. At my suggestion he used histamine and worked to find how far from this patch of skin the action would take place. He tells me that it was distinct for at least 170 millimetres. The most extensive histamine flares I have witnessed from single punctures have been 60 and 70 mm. in radius and they are more usually confined within 20 or 30 mm. radius. I have seen flares from stroking extend as far as 140 mm. from the line of the stroke. It is clear from these observations that the nerve channels covered by the reflex may be of considerable length.

The arteriolar termination of the reflex. In Chapter III evidence has been given to show that the flare is due to opening up of the strong arterioles ; upon these, sensory nerve endings from collaterals are known to exist (*270*).

It has been suggested that the reflex innervation proceeds farther, and that the capillaries are involved actively. A very faint and widespread flush is sometimes seen on the skin of the arm around a point stimulated while the circulation is under arrest (*214*), especially is this so if the limb hangs down ; and the area of this flush may be found to correspond to that of the flare on release. Though I have seen this ghost-like flare on occasion,

I am not entirely convinced that it means active dilatation of the corresponding minute vessels. It is true, however, if the circulation to the skin is stopped after a full flare has appeared, that its outlines remain distinct and, if the blood is massaged away from the affected skin, the flare reappears as the blood returns. It reappears very slowly, however, and is less distinct than previously.* The manner in which an arteriolar flare fades, being broken up by increased minute vessel tone, definitely precludes an energetic contribution of the minute vessels themselves to the preceding vasodilatation. Evidence that the minute vessels are involved actively in the reflex is consequently unsatisfactory ; the facts certainly warrant the conclusion that any active dilatation occurring is inappreciable.

In this connection it is of interest to note that while sensory nerves have been traced to terminations on arterioles, they are not found on the minute vessels (*270*).

Distribution of the axon reflex mechanism. The sensory axon reflex here fully described is not witnessed on the surface of the abdominal viscera according to Ebbecke (*75*), and Florey (*85*) failed to find it in the pia mater. It seemingly forms a mechanism of defense peculiar to superficial and sensitive structures, such as the skin and conjunctival sac.

Innervation of capillaries.

Experiments upon human skin, apart from the observations just discussed, have thrown no light on the innervation of capillaries.† It is known that capillaries and minute venules are accompanied by non-medullated networks and spiral filaments, and such have been described in the human skin by Gläser (*94*). Actual terminations in the capillary walls have not been observed. The most recent account of these non-medullated nerves is by Stöhr (*236a*) who describes the fibres to human capillaries as branching, forming tangles around neighbouring cells and sending occasional loops around the capillaries. He likewise fails to find free endings.

Steinach and Kahn (*233*), in their observations upon the capillaries of the frog's nictitating membrane, repeatedly saw the capillaries contract after a latent period of some 15 seconds on stimulating the sympathetic

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* An area of local dilatation of the minute vessels similarly treated reappears quickly and fully and is much more precisely defined at its old margins. Both observations should be carried out in a way that ensures that an appreciable pressure remains in the veins on occluding the artery ; the return of blood to the skin rendered pale being thus encouraged.

† An observation by Leriche and Policard (*155*), that has been cited in this connection, is as follows. They notice an abrupt diminution in the size of the capillaries of the nail bed on mechanically stimulating the adventitial coat (in which lie sympathetic fibres) of the brachial artery. Since, in the same paper, they state that this procedure causes a tense contraction of the artery locally, the effect on the capillaries of the finger is to be regarded as a simple passive effect.

nerve. This observation is the more noteworthy because it was made after the heart had been removed, thus eliminating passive effects. Evidence confirming this vasoconstrictor supply to the capillaries has been brought forward by Hooker (*120*) and by Krogh, Harrop and Rehberg (*139*). The former studied the cat's ear, the latter the frog's web. In these last experiments, however, it is not entirely clear that the effects witnessed may not have been, at least in part, passive and attributable to corresponding changes in the arteries.* Harris and Marvin (*107*) at my suggestion, have recently investigated the response of the capillaries of the rabbit's ear to cervical sympathetic stimulation. They find that this stimulation causes the blood to be expelled from the capillaries after the circulation in them is brought to complete standstill by compressing the arteries supplying the ear. This evidence is the clearest we possess of a vasoconstrictor supply to capillaries in mammals.

The evidence for a supply of vasodilator nerves to capillaries, evidence alone relevant to the matters discussed in the previous section, is much less certain. It has been brought forward by Doi (*66*) and Krogh (*135*), and confirmed by Krogh, Harrop and Rehberg (*139*) and by Langley (*143, 144*). All their experiments were upon frog's web or tongue, with the exception of those of Langley upon the cat's paw. They are fundamentally alike, in that vasodilatation in skin or mucous membrane is seen to follow peripheral stimulation of the posterior root ganglia or of sensory nerves.† Such a procedure, as we have seen, dilates the vessels in the corresponding peripheral area, and the experiments of these workers were brought forward to show that endothelial vessels, including capillaries, are actively involved in the reaction.

The possibility of passive effects is discussed and excluded in most of these experiments ; thus Doi first dilates the arterioles by means of acetylcholine and subsequently obtains capillary dilatation, while the arterioles show no further change, upon stimulating the posterior roots. Langley used our occlusion test, and saw the cat's paw flush on stimulating cutaneous nerves distally, during the circulatory arrest. Marvin and I have confirmed this upon cats in which the sympathetic nerve had been caused previously to degenerate (*172, 173*).

It clearly appears, therefore, that an active dilatation of capillaries may result from nerve stimulation. The impulse is conveyed, certainly in most and probably in all of the instances cited, antidromically through sensory nerves. In these experiments however, the impulse is not conveyed immediately to the capillary wall. The vasodilatation is produced indirectly by a release of H-substance in the skin and this substance proceeds to act upon the vessels locally. This harmonises with the observation that medullated nerves do not extend to the minute vessels (*270*).

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* As in the case of arterioles, the supply is sympathetic and a tonic effect seems to be exerted.
† In Krogh's experiment the lingual nerves were used.

The antidromic impulse and axon reflex related.

It will be clear from the facts already set forth that the antidromic impulse and that of the axon reflex utilise similar sensory paths. The two mechanisms seem closely inter-related, and the paths are indicated in the accompanying diagram (Fig. 68). According to the views expressed, the antidromic impulse passes down the sensory nerve and is conveyed to the skin by a collateral branch. This channel of conveyance is represented by an unbroken arrow in the diagram, and the nerve is shown as breaking up into an

SENSORY NERVE

CONSTRICTOR

ANTIDROMIC

ARTERIOLE
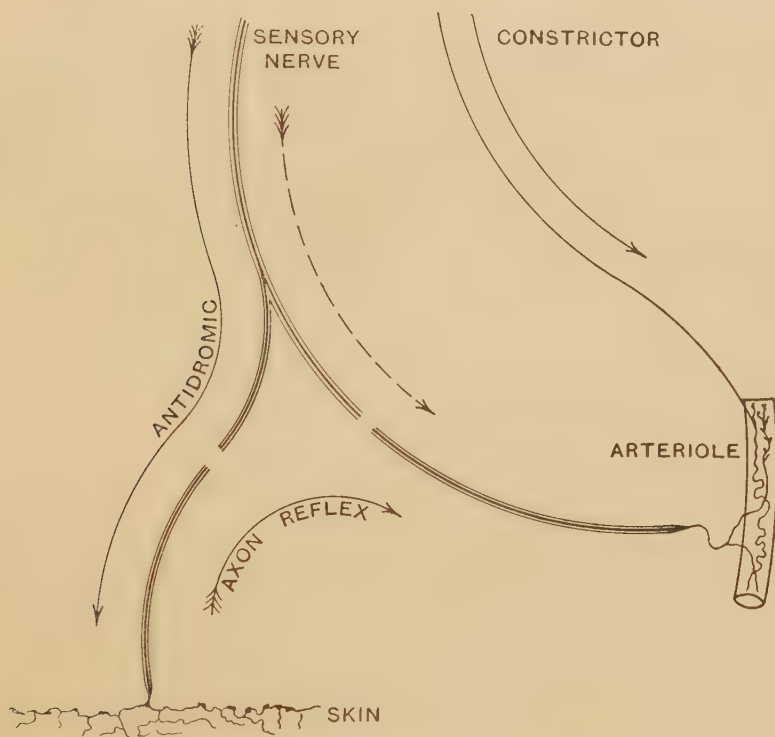
AXON REFLEX

SKIN

Fig. 68.

arborisation of nerve fibrils in the superficial layers of the skin. The impulse of the axon reflex is conveyed up a sensory collateral and passes back through an arteriolar collateral to its termination. Here it is to be remarked that we should be unwise definitely to assume without further evidence that the same cutaneous collateral is traversed by both forms of impulse, though for simplicity I have so represented it in the diagram. The forms of sensory termination in the skin are numerous, and distinct kinds may possibly subserve the two functions.

There is insufficient evidence that the antidromic impulse is conveyed along the arteriolar collateral, the path marked by the broken arrow, though observations by Doi (*66*) and by Feldberg (*82*) seem at first sight interpretable in this way.   Doi brings evidence that during antidromic stimulation the arterioles, as well as the minute capillaries, may dilate.   He does not say specifically that these arterioles are coated by muscle, though this is to be inferred from his statement that they are vessels upon which histamine exerts a constrictor effect.   Feldberg states that antidromic stimulation dilates the central artery of the rabbit's ear.   These observations still do not show that such arterioles respond directly to an antidromic impulse.   The antidromic impulse releases H-substance in the skin ; all the minute vessels in the corresponding territory will dilate as a consequence, and this may be regarded as the chief vasodilator action.   But if the concentration of the substance rises to an adequate point it will act, not only upon the minute vessels, but also upon the sensory nerve endings, and will produce through the channel of the axon reflex, as does H-substance when liberated in the skin by physical injuries, a dilatation of distant arterioles.   This possibility requires consideration and further investigation.

CHAPTER XVI.

REGULATION OF BLOOD FLOW BY VESSELS OF DIFFERENT

CALIBRE.

IN considering the influences that cutaneous vessels of different calibre exercise upon blood flow, it is impossible to deal in absolute terms, since the quantity of blood passing through a given area of skin in a given time is not as yet measurable. It will be convenient to start from a middle point and to speak of an *ordinary flow* to the skin. By an ordinary flow, I mean the flow that prevails when a man, lightly but warmly clad, has been for some while at rest at room temperatures of about 18° to 20°C. In these circumstances, and in normal people, if a portion of the skin, such as that of the arm, has been exposed for examination, its temperature is usually about 29° to 32°C. In the arm as a whole, at these temperatures, the flow is usually between 2 and 5 c.cm. per 100 c.cm. of tissue per minute and, as has been seen earlier, the capillaries of the skin, with a few possible exceptions, are known to be open. Their sizes in these conditions vary in different parts of the skin, but in that of the limbs their diameters are usually between 0·005 and 0·01 mm. Thus, they are capable of conveying blood corpuscles in single file, undistorted or with slight distortion.

This ordinary flow may change ; it may decrease or increase. The influence that vessels of different calibre exert upon the cutaneous blood flow in these two directions will be considered in the present chapter ; the vessels discussed will be the strong arterioles on the one hand and the minute vessels, including the terminal arterioles, on the other.

Decreased flow.

The strong arterioles. I think we may conclude that the strong arterioles of the human skin are capable of contracting almost if not quite to obliteration. The strongest evidence for this statement is found in the reaction to cold ; in this all the minute vessels are demonstrably dilated, while the rate of blood flow through them is almost negligible. Although some contraction of the subcutaneous veins occurs simultaneously, it can scarcely be held to play much part in regulating flow, for the walls of the vessels are less thickly coated with muscle than are those of arteries of corresponding size, and an almost complete obstruction in deeply seated veins is inconsistent with the

sharp correspondence between the area of minute vessel dilatation and the area cooled.

Minute vessels. It seems equally certain that, by contracting, the minute vessels can themselves bring about a similar result. Thus, in the white reaction described in Chapter II, and produced by lightly stroking the skin, the minute vessels of the skin become lost to view ; in this reaction, and in that following adrenalin puncture, contraction is sufficiently powerful to resist the flood produced by full dilatation of the strong arterioles, for example in the histamine flare, and to meet and hold very considerable pressures imposed from the venous side, (see page 32).

Increased flow.

The strong arterioles. The vessels that are most capable of increasing the flow of blood to the skin beyond its ordinary level are the strong arterioles.

Cent.
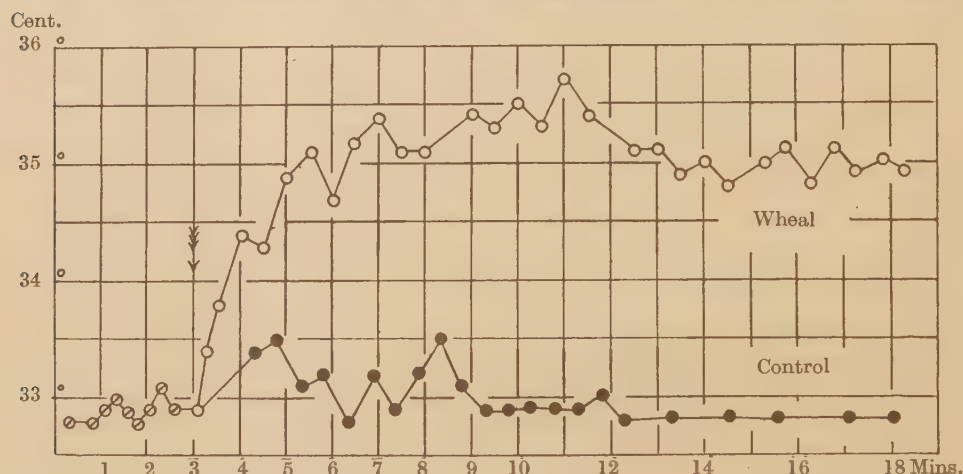
Fig. 69. A chart showing the change in temperature of the skin after stroking it heavily. From a case of urticaria factitia. Rectal temperature 37·6°. The divided circles represent the temperature of the skin of the back before stroking and were taken alternately from the area to be stroked and from that subsequently used as the control area. The arrow indicates the time of stroking and the plain and black circles represent the subsequent temperature of the vividly reddened skin immediately bordering the line of stroke and of the control skin, respectively.

Only vasodilatation of the arteriolar type brings the skin to a brilliant and persistent red colour and greatly lifts its temperature. The cutaneous temperature is often raised by 1° or 2° (from 31° or 32°C) by such a flare as is produced with one or several closely set histamine punctures (*160*). In a case of conspicuous urticaria factitia the skin temperature, adjacent to a forming wheal produced by stroking, rose as much as 2·5° (from 32·8°C) and reached a point within 2° of rectal temperature (Fig. 69). Equal lifts have been seen when the skin has flared similarly to other forms of stimulus.

Normally, at room temperatures of 17°C, the temperature of facial skin lies about 4° below rectal temperature. In bright flushing of the face the difference falls to 3° or less. In a case of unilateral cervical sympathetic palsy (see page 269) the normal side of the face presented an average temperature of 33·5°C and the affected side a temperature of 34·7°C (rectal temperature being 37·6°C). It is probable that, starting from the normal facial temperature of 32° or 33°C (with rectal temperature of 37°C), a rise of 1·5° to 2°, or an actual temperature of 34° to 35°C represents a full or almost full vasodilatation of the facial skin vessels (*160*).
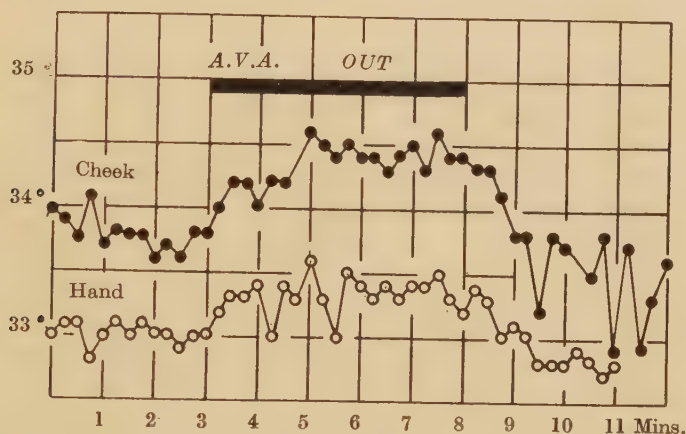
Fig. 70. A chart showing the effect of closing the artery leading to an anastomosis of the superficial femoral artery and vein (*A. V. A. out*) upon the temperature of the cheek and palm of the hand. The two observations were made separately, but have been charted together, the femoral artery being occluded on both occasions for exactly 5 minutes. It is to be noted that, although the increased and decreased blood flows to the skin begin abruptly, neither the rise nor fall of temperature is completed under 2 minutes.

An idea of what such temperature changes as are here discussed may signify in terms of blood flow may be gathered very approximately from the following observations on a case of arteriovenous anastomosis. In this patient a bullet wound had freely united the superficial femoral artery and vein. It was found that, by compressing the common femoral artery, and thus cutting the anastomosis out of the general circulation, the blood flow to the arm, repeatedly estimated plethysmographically, could be doubled at will (*163*). When the circulation in the vessels of skin, represented by the long capillaries of the finger nail bed, was watched in similar circumstances, flushing of these and a conspicuous rise in the rate of blood flow in them could be seen, showing that these vessels shared in the increased supply.* The increased blood flow was correlated with the corresponding rise of

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* It should be noticed that, in arguing from whole limb to skin there is no real security from the standpoint of quantity, and the values given later can be regarded only as very tentative.

temperature (*160*) as illustrated by Fig. 70. The rise of temperature consequent upon cutting out the anastomosis amounts to 0·4°. If we assume that a rise of temperature of 0·4° (from 33° with rectal temperature at 37°C) approximately corresponds to a doubled flow of blood, then a rise of 2° from 33°C would represent, not a fivefold increase but one considerably greater in extent. Each increment brings the temperature of the skin nearer to that of the entering blood, and the last will never be attained however fast the blood moves. When with the flare to injury the temperature is lifted by as much as 2·5° (Fig. 69), and attains such levels as 35·3°C (2·3° below rectal temperature), the rate of flow through the skin must approach its maximal value.

Such briefly, are the indications that we possess of the effects of dilatation of the strong arterioles.

It is important to remark, however, that such arteriolar dilatations as are here described are accompanied by passive widening of the minute vessels of the same territory ; thus the effects are really those of dilatation of all the cutaneous vessels.

Minute vessels. When the minute vessels dilate fully and together, they produce at first a bright redness, which in its depth rivals, if it does not surpass, that of the flare just described ; but the bright colouring is short lived, the skin soon assuming a bluer tint. This is the purely local reaction in which the strong arterioles are little if at all involved.* The temperature of the skin following such a local reaction, for example after the stroke or the freeze, and taken at a stage when any surrounding flare that may have been associated has subsided, is found to lie not more than 0·5°C at the most above that of control skin ; the temperatures of the deeply reddened and the unaffected skin are generally alike or the former is perhaps 0·2°C the higher.

When, a day or two after the skin has been frozen, it presents a deep local reddening, it is easy to determine by using transient pressure or by microscopic examination that its minute vessels are carrying blood freely ; but the flow through them is insufficient to raise skin temperature.

The same statement applies to the deep reddening that appears within a day of an ultraviolet burn. In both instances venous congestion, a more delicate test, will demonstrate some increase of blood flow, the affected area becoming pink upon a cyanotic background. Even this sign disappears at a later stage, and it is often lost long before the natural skin colour is resumed.

Thus, it seems clear that dilatation, even wide dilatation, of the minute vessels from an ordinary state, produces much less effect on blood flow than

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* The contribution of arterioles to reactions of this kind is previously discussed (page 41). It is possible that the vessels of the subpapillary arterial plexus contribute here and in the local response to injury, but that, owing to their greater distance from the epidermis, they are less exposed to vasodilator substances released and therefore respond more transiently. The actual degree to which these vessels are affected is unknown.

does a corresponding dilatation of the strong arterioles. In explaining such increase of flow as occurs when the former vessels are involved, we should probably turn first to the terminal arterioles, for these vessels are of much the same narrowness as the capillaries into which they break, and in which the flow is therefore much slower; friction in these arterioles is therefore relatively great and resistance high.*

There is one example of minute vessel dilatation of which more is to be said in this connection; it is reactive hyperæmia. Were we to assume that
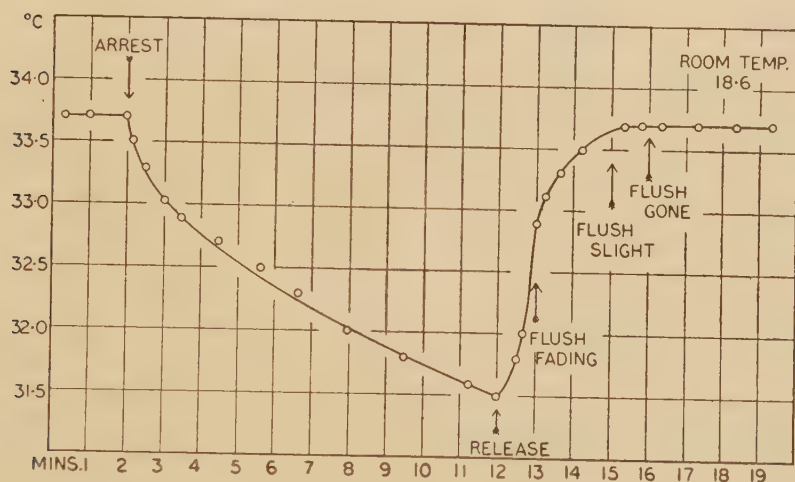
Fig. 71. The effect upon the subcutaneous temperature of the warm arm of arresting and releasing its circulation in a still room at 18·6°.

the increased flow to the skin is similar to that in the whole limb, we should be forced to acknowledge almost a tenfold increase in the rate of blood flow as a not uncommon after effect of a 10 minute circulatory arrest (see page 160). An increased rate of blood flow through the skin itself in reactive hyperæmia may be recognised microscopically in the bed of the finger nail. The ordinary flow in the vessels of the finger is here moderate and uninterrupted, though its rate lacks uniformity in different capillaries. Within 15 or 20 seconds

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* At the same time it is possible that dilatation confined to a capillary increases flow, such may be inferred at all events from Heimberger's observations (*112b*). He strokes the capillary loop through the skin of the nail bed and observes dilatation and increased flow in this vessel. I am not sure, however, of the meaning of this observation; the stroke empties the vessel and it immediately and rapidly refills. An initial and transient reddening of the skin of the limb that sometimes precedes the white reaction to stroking, and that was first noted by Carrier (*43*), probably belongs to the same category.

of the release of an occluded brachial artery the current becomes very rapid in all the capillaries.

Temperature changes in the skin during this reaction have been studied for the purpose of comparing the increased flow with that presented by local reactions previously described. If the skin temperature is taken continuously, it is found to fall steadily during the period of circulatory arrest (Fig. 71), the rate of fall depending on room temperature, upon atmospheric humidity and other factors. The rate of fall is greater in the case of a digit than in the case of the arm (*see 30*), for the surface of a finger is greater relative to its mass. When the circulation is released, the curve returns to, but will not pass beyond, its original baseline ; thus at no stage is the loss of heat during the period of circulatory arrest more than compensated for by the subsequently increased flow. If the surface temperature of the human limb is maintained constant until the release, there is again no rise, or at the very most a rise of a quarter of a degree,* either in subcutaneous or in surface temperature, although the release has followed arrest lasting as long as 10 minutes. Thus the temperature records agree with those obtained when the minute vessel dilatation occurs in response to other forms of interference.

How is this observation to be rendered compatible with the greatly increased flow that, as we have seen, occurs to the limb as a whole ? There are several factors that render the comparison difficult. Firstly, although surface temperature is maintained, the limb as a whole loses heat during the circulatory arrest ; the first blood to flow to the skin is a little chilled ; and when hotter blood comes it gives up more of its heat to the deeper tissues than usual. Secondly, the rate of flow to the limb as a whole, though at first greatly increased, rapidly declines ; 2 minutes from the release it is usually no more than 50 to 100 per cent. above the ordinary value in the limb as a whole. The delayed influence of such a decline on skin temperature is shown by Fig. 70, page 227. Continuous temperature records of the skin were taken from this patient, and the rise and fall are related in this chart to blood flow ; the rate of flow is known to have changed instantly with compression or release of the femoral artery, but the rise of temperature occupies 2 minutes and the fall fills an equal time period. Thus the initial flows in reactive hyperæmia are not fully reflected in the temperature curve.

In reactive hyperæmia the apparent discrepancy between temperature change in the skin and blood flow to the limb is in part accounted for by these considerations, though it seems improbable that it can be explained entirely in this way. It seems likely that the volumetric measurement of flow to the

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* In practice it is difficult to be sure of temperature changes of less than a quarter of a degree. This is so because the skin lacks uniformity of temperature, both from time to time and from place to place.

whole limb considerably overestimates the increase of flow to the skin in this condition.*

Summing up, it may be said that if the vessels are carrying an ordinary amount of blood, as defined earlier in this chapter, then change in the direction of increased flow is mainly under the control of the strong arterioles, while decreased flow may be brought about either by the strong arterioles or by the minute vessels, acting separately.

A point that has been raised by Burn and Dale (*37*) requires brief comment. It has long been known that in the frog's web the diameters of many of the minute vessels may be less than that of the blood corpuscles about to pass through them and that the blood cells may be squeezed and deformed in the capillaries (Lister *177*). The fact has been displayed well by Krogh cinematographically (*137*), and the suggestion is that the blood encounters in these vessels a material part of the total peripheral resistance. The question comes as to whether a similar phenomenon is common in the minute vessels of the human skin. In the peripheral circulation of cold-blooded animals this squeezing through of blood cells is seen in capillary fields in which only relatively few vessels are open at a given moment. The last state, as has been seen, does not prevail in the human skin in ordinary circumstances.

Measurements of the diameters of living capillaries in the human skin, especially of the pale skin of the arm, though they cannot be accomplished with accuracy, often come near to the value 0·005 mm.; the usual diameter given for red blood cells when shed is 0·008 mm. When, in the capillaries of the arm, the movement of the blood can be well seen—and this admittedly is not often—it appears to be quite free, and white cells are seen to pass frequently and without hindrance.

Another phenomenon, associated with narrow arterioles or capillaries and described by Lister (*177*) and by Krogh (*136*), is called by the latter " plasma skimming," which means that red cells are unable to enter a capillary that still allows the fluid plasma to pass; when this occurs, the capillary becomes temporarily invisible. In human skin under ordinary conditions I have seen this happen very rarely; a filled capillary springs into view abruptly and then vanishes; when I have seen it, the change has been repeated at very brief intervals of time and almost rhythmically.

From these considerations, and especially from the evidence that dilatation of the minute vessels from the ordinary state does not greatly increase the rate of flow in them, it seems to me improbable that friction in the capillaries of the human skin can, in the absence of unusual tone, contribute greatly to peripheral resistance.

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* For this reason the comments upon the rise of temperature in Fig. 70 and the associated increase of blood flow to the skin, must be read critically, and the values that are given, and that tentatively relate the two, are to be regarded as no more than indicative.

CHAPTER XVII.

A GENERAL SURVEY OF H-SUBSTANCE ACTIVITIES AND THEIR BALANCE.

In early chapters of this book the responses of the cutaneous circulation to injuries have been considered. In the last three chapters we have discussed the cutaneous blood flow from three separate standpoints, namely, its physiological regulation by local metabolism, its regulation by nervous impulses, and the regulating parts played by two classes of vessel.

In the present chapter I propose to consider the regulation of cutaneous blood flow as a whole, so as to correlate the more important problems hitherto discussed.

Local metabolites.

The theory that substances released by the tissue cells influence the cutaneous circulation has been formed around evidence, a description and discussion of which forms the chief subject matter of this book. Reactions of the skin to numerous influences, to various forms of physical or chemical injury, to warmth, to circulatory arrest, and to antidromic nervous impulses, have been considered as individual problems. Here and there the response to one influence and another has been correlated briefly. It may help to render the theoretical inter-relation of the problems clearer if I here set down in more deliberate order the conclusions at which we have arrived, or to which we are tending, weaving these into a more general conception.

In Chapter XIII evidence has been brought forward to show that the tissue spaces of the skin are constantly receiving a substance causing the minute vessels to dilate. This substance is a product of normal metabolism. It serves to direct blood particularly to those parts of the skin in which metabolism is most active. It serves further to restrain unnecessarily free blood flow to parts of the skin to which an excess of blood has been forced; the latter influence is accomplished by the lowering of the substance's concentration in the tissue spaces, the substance being removed by the free stream of blood through the vessels of the region ; * other influences presently to be discussed, and tending to produce constriction of the minute vessels, now exert a more unopposed and effective influence.

An increase of the skin's temperature will increase its activities and will lead to a more rapid outpouring of the vasodilator substance, a moderate

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* Here the probability of simultaneously increased lymphatic flow is also to be remembered (see page 238).

decrease of temperature will have the reverse effect and so the size of the minute vessels and their blood carrying power will be proportioned to such variations in cellular activity as are brought about thermally.

When the circulation to the skin is stopped or is impeded, the vaso-dilator substances will continue to pass into the tissue spaces, there to record in proper measure a debt against the circulation and by their continued presence insistently to call, then and later, for this debt's discharge in full. The rate at which these substances pass into the tissue spaces will tend to decline as the circulatory arrest is continued, because cellular activity will tend to decrease.

The cells of the skin are regarded as reservoirs, and an increase in the permeability of their walls, such as may be supposed to accompany metabolic activities, will lead to the oozing of the vasodilator substance into the tissue spaces.

In discussing the responses of the skin to a number of injurious physical agencies that act abruptly, we have come to the conclusion that these responses are due to a substance preformed in the cells of the skin, and that this substance is liberated at once in considerable concentration by the stimulus applied (see page 128). According to my general conception such liberation will naturally follow if the agency applied ruptures the cell wall or if stimulation greatly increases the permeability of the cell wall. We have termed the released substance the H-substance in this instance. Finally to prove that this H-substance is identical with the metabolite normally and continuously released by the cells into the tissue spaces, is perhaps impossible upon present evidence. Nevertheless this evidence, when regarded as a whole, strongly favours the view, and is seemingly nowhere incompatible with the corresponding conclusion. We may to advantage briefly state the most striking parts of the evidence and the most cogent arguments.

The vascular response to a small or slow outpouring of H-substance and that to the physiological metabolite are similar in quality, affecting as they do the minute vessels only over the precise area coming under the new influence. Thus circulatory arrest, or warmth applied to the skin, leads to local dilatation of these vessels, as does stroking the skin or light freezing. In all these instances the reaction is one passing away very gradually, over a time interval measured by very many minutes. In each instance this gradual fading away is attributed to the gradual elimination of a substance concentrated in the tissue spaces, the rates of removal being in general compatible with the removal of one and the same substance.*

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* Many of the conclusions and reflections of this chapter are applicable to other tissues of the body. Gaskell believed that the increased flow of blood to muscles that are contracting is directly governed by acid metabolites released in the muscle. Grant and I (*165*) were much impressed by, and called attention to, the very slow decline of this vascular response in muscular exercise. Contractions of the forearm muscle, lasting for 2 minutes, are accompanied and followed by an increased blood flow to the limb lasting altogether 12 to 16 minutes. It seems difficult to believe that products as diffusible as lactic acid require so long a time for their elimination. I suggest that in this instance H-substance may possibly be a chief agent responsible.

If we are led to conclude that there exists normally in the cells of the skin a regulating substance capable of exerting a vasodilator action when released slowly and continuously into the tissue spaces, then we can scarcely escape concluding also that any physical damage such as is capable of rupturing, or increasing the permeability of, the cell wall will release this substance and that it will act promptly, causing at least a dilatation of the neighbouring vessels. We have already arrived, on the independent evidence of brief latency, at the idea that in physical injury a substance preformed in the cutaneous cells is released.

The reaction to increasing temperature is especially to be emphasised. The clothed skin has a normal surface temperature of about $34°C$; at $36°$ to $38°$ it definitely reddens, at $43°$ to $44°$ it begins to show the second member of the triple response, namely, the flare. The necessary rise is so slight that to postulate a new intervening factor becomes gratuitous; there is an insensible passage from effects that are clearly due to normal tissue processes to effects hitherto regarded, and apparently on no very logical grounds, as strictly separable.

The example of reactive hyperæmia may be interpreted to point in precisely the same direction, namely, that if metabolites normally oozing into the tissue spaces are made to concentrate there by holding up the blood flow that normally washes them away, this concentration will cause at first simple local reddening; but if the concentration is allowed to become great the remaining parts of the triple response will be seen.

Thus, the examples of heat and of circulatory arrest suggest that excessive accumulation of the normal metabolites sets up the more violent and complex vascular reaction that we have previously associated particularly with injury.

Another and very significant illustration is that of antidromic nerve action. We know that by this means a simple local vasodilatation may be produced in the minute vessels of the skin, and the example of herpes zoster suggests how this may become converted into the fuller and destructive response. The importance of this example lies in the responsible substance being released through purely physiological channels. Are we here to postulate the release of an abnormal substance? On the contrary are we not forced to the view that the substance is a natural one, liberated in excess?

Now a substance having precisely the actions required by the theory, one which calls forth the full triple response, is recoverable from the tissues. Histamine was first isolated in pure form from the mucous membrane of the bowel by Barger and Dale (*10*). Later Abel and Kubota (*1*) recovered small quantities of it from a preparation of pituitary gland and from the gastro-intestinal mucous membrane and obtained suggestive evidence that a similar or identical substance can be extracted from muscle and from liver. Most recently, Best, Dale, Dudley and Thorpe (*20*), in their very important work, have recovered the substance in large quantities from the lung and from the liver. In the former organ the concentration is approximately 1 in 13,000, in

the latter approximately 1 in 200,000. These data are of high significance. Not only is the substance present in the tissues, but it is present in concentrations adequate to dilate any minute vessels with which, on release, it may come in contact. So far, histamine has not been recovered as such from skin ; actually the attempt to extract it has not yet been made ; but there is little reason to doubt that it will be found there. There is a natural vasodilator substance in skin and it can be assayed physiologically by a method described by these workers. Observations in my laboratory by their method have shown its concentration in human skin, in terms of histamine base, to be about 1 in 60,000. The same extracts of skin, when pricked into the living skin, give rise to the triple response (including wheal and flare).

With this series of facts before us it is difficult to refrain from stating without reserve the simple conclusion that the vasodilator substance considered and the H-substance are one and the same, and that this substance is histamine, free or held in loose combination. This conclusion would harmonise with the chief evidence at all points. It is to be pointed out, however, that so stated it would fail to take into consideration the disintegration products of dead or dying cells. These supplementary and hypothetical substances may themselves include histamine, they may include bodies closely allied chemically or having similar actions.

It is not *essential* to assume the presence of disintegration products of this kind even in the case of such severe injuries as freezing and burning. The participation of such products can hardly be supposed in the development of herpes zoster, for this supposition would reverse the order of events. The evidence goes to show that the release of H-substance is the first event ; this calls forth a vascular response, which, if full, leads to exudation and disruption of the tissues. Thus, in this instance it is wrong to regard either the tearing of the tissues, or the death of cells that results, as the cause of the vascular reaction ; on the contrary these injuries are here its effects. Nevertheless there are instances of response to skin injury in which disintegration products cannot be neglected entirely as a possible factor. It is desirable that they should still be remembered and further considered, and for this reason I shall continue to refer to H-substance in preference to histamine.

Regulation of cell output. The oozing of our substance, so I suppose, is in part controlled physiologically by impulses descending the sensory nerves antidromically. Whether these nerves control actual metabolites in the cells or whether they exert a direct influence upon the perviousness of the cells' boundaries is largely conjectural, though the former view seems the more probable. It is clear that loss of the sensory nerve supply to the skin will rob the skin of any control such as may be exerted through these channels. It seems probable that certain cutaneous disturbances, such as glossiness of the skin, that are connected with degeneration of the sensory nerves and comprised in the adjective " trophic " result from this loss.

It would be interesting to speculate upon why the skin is so endowed with this antidromic governance of its functions.* I believe that it may have a far deeper significance than has as yet been realised; thus it may conceivably be associated with the needs of rapid and frequent repair of the epidermis by cell multiplication.

Elimination from the tissue spaces. Such evidence as we possess goes to show that when the H-substance passes into the tissue spaces, it subsequently leaves these by two channels, namely, the vascular and the lymphatic. When, in my observations with Miss Harmer (*170*), we obtained a general circulatory reaction by stroking the skin of an urticarial subject, the earliest evidence of a reaction was seen to come within the space of 2 or 3 minutes, a time period too short for the substance to pass by way of the lymphatic channels into the blood stream. The time period is similar if histamine is introduced in comparable quantity subcutaneously; with heavier dosage it comes earlier (*106*).

If a small quantity of histamine is introduced intradermally it may be shown to spread along the lymphatics, for the skin over these reddens and wheals (see page 122). A similar spread of our vasodilator substance has been witnessed in the case of ultraviolet light injury and freezing.

The visibility of lympathic spread is in itself of interest, for this implies that although lymphatic channels are entered, the substance does not remain confined to them but oozes through their walls and makes contact with surrounding vessels. Thus much of the substance that enters the lymphatics will not pass on into the main ducts, but will be picked up by the blood vessels before it reaches them. Thus the lymphatics serve not only to conduct away tissue lymph but to expose this lymph to a greater vascular surface.

Vessels directly involved by the H-substance and their influence. Before leaving the consideration of the local metabolic control of blood flow, it is to be emphasised that this regulation concerns especially the minute vessels of the skin, namely, the terminal arteriole, the capillary proper, the minute venules and very possibly the subpapillary arteriolar plexus and deeper venules. The vessels known to be involved are all simple endothelial tubes and, as has been said earlier, are affected alike by any substance that acts in a particular way upon any one of them. It is presumed that through the simple walls of all these endothelial vessels, exchange takes place between the blood and the tissue spaces; they are all vessels therefore that will tend particularly to come under the immediate influence of tissue metabolites.

In the skin, as the last chapter has shown us, these minute vessels are capable of reducing the blood flow to a negligible quantity. They are capable of opening up from their ordinary state and of thus bringing increased flow to the tissues locally; it is questionable however if they are able to bring a sustained flood of any considerable magnitude, unless their dilatation is

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* From Bayliss's observations (*12*) it would appear to be specially endowed.

accompanied by simultaneous widening of the strong arterioles that supply them. Such arteriolar widening will only result if the concentration of H-substance in the tissue spaces rises sufficiently to stimulate the cutaneous sensory nerves.

Relation of H-substance to control by circulating hormones.

The regulation of the peripheral circulation by hormones in the blood stream is a question that does not come properly within the scope of this monograph. I shall consider it only briefly.

Two vasoconstrictor hormones are known and are widely regarded as normally influencing the tone of the blood vessels. So far as adrenalin is concerned its presence in the blood stream in concentration adequate to constrict arterioles or minute vessels remains perhaps still uncertain. Recent work lays greater emphasis upon a circulating pituitary hormone. Thus the observations of Hogben and Winton (*118*), and of workers cited by them, show that a hypophyseal secretion governs the pigment melanophores of the frog's skin, and the conclusion is reached that the corresponding hormone normally circulates. Similarly Rehberg discovered that extirpation of the gland causes loss of capillary tone in the frog, work followed up with, and extended by, Krogh (*137, 140*). Krogh regards pituitary hormone as the chief regulator of capillary tone, a matter discussed at length by him in his book (*137*); and he has recently brought evidence that the blood issuing from the jugular vein of the horse contains more of this principle than does blood ascending from a limb (*138*). Likewise Verney (*254*) by studying the rate of urine flow, has provided very convincing evidence that a pituitary hormone normally circulates in the mammal and controls renal secretion. Pituitary extracts when introduced into the general circulation of man exert a powerful influence upon the cutaneous vessels, producing conspicuous blanching of the skin (*164, 223*).

Sacks (*223*) working at my suggestion, collected evidence to show that it acts most forcibly on the minute vessels of man, contracting them and decreasing their permeability ; the last observation may be said to harmonise with Pohle's discovery that removal of the hypophysis leads to œdema in frogs (*206*).*

I refer to these observations because, in thinking of the local metabolic regulation of blood flow, it is important that the possible influence exerted by vasoconstrictor substances in the blood should be borne in mind. The influence is rarely relevant to the subjects discussed in this monograph. It was relevant in the case of reactive hyperæmia, and has been dealt with in that connection (page 179). In this instance, be it observed, the tendency will be for the hormonal factor to act in harmony with that of local metabolic accumulation ; for when the circulation to the skin is arrested, the skin

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* It is to be remarked, however, in this connection that in hypopituitarism in man, although large quantities of urine may be passed, œdema is not a symptom.

loses its supply of vasoconstrictor substances. If a withdrawal of natural vasoconstrictor substance plays any part in this reaction, it is an inappreciable one, being overshadowed by the local metabolic factor.

When, if ever, the two factors work in conflict, the local metabolite will tend to dominate the situation ; it constitutes the more powerful influence. Thus if a full local dilatation of the cutaneous vessels is obtained by the release of H-substance in injury (or by histamine itself) this response cannot be broken down either by pituitary extract or by adrenalin in powerful solutions. On the other hand if the constrictor effect is primary and full, it is broken down by the same vasodilator agencies (see page 245). Further, there is evidence that if the minute vessels have reacted partially to our H-substance (or to histamine), they become less susceptible to the vaso-constrictor hormones. A possibility that should be considered is as to whether or not local diminution of H-substance, such as occurs when blood flow is increased, may cause an increased susceptibility of the minute vessels to circulatory vasoconstrictor substances, and thus be in part responsible for the very high tone of these vessels that is apt locally to prevail in these circumstances.

Krogh's view that pituitary hormone forms the chief regulator of capillary tone may be true if it is confined to substances circulating in the blood stream. The evidence is decidedly against his contention that it chiefly regulates local flow ; that function is mainly served by our H-substance.

In what concentration this substance normally enters the general blood stream, there to be opposed by the action of vasoconstrictor bodies, is un-known, but it may be supposed that one important part played by the constrictor substances physiologically is to counterbalance the vasodilator bodies entering the circulation from the tissues of the body in general.

Regulation of lymph flow.

It would be unwise to complete this chapter without referring at least in general terms to a problem closely interlocked with those here considered, namely, the regulation of lymph flow. In this direction I have made few personal observations and do not feel justified in writing upon it more than briefly. It will be manifest, however, that since histamine is known to increase the fluids of the tissue spaces, and since almost all the influences described in this book as playing on the minute vessels and dilating them are known, from direct observation of the skin, to increase tissue fluids locally, or, from observation of the lymphatic ducts, to increase the lymph flow, it is obviously suggested that the same fundamental mechanism is called into play and governs locally both the flow of blood and transudation through the vessels.

Tissue metabolism, the blood flow *to* the part, the lymph flow *from* the part are activities, so one would imagine, which to be effective must be concerted, under the same nicely regulated controls. This natural inference suggests a renewed and searching analysis of the factors underlying lymph

flow, inquiring into the influence of the substance histamine upon it, and into its possible governance by the nervous system and, especially in the skin, by antidromic innervation.

The observations here described and the conclusions drawn from them should not be allowed to rest at the points to which they have been taken, they should be correlated with the physiological movements of fluid through the tissue spaces and, where this proves possible, with the remaining phenomena of the complex processes now summed up in the words *inflammation and repair*.

Regulation of blood flow reviewed.

The last chapters have been devoted to considering the mechanism governing the blood flow to the skin. There is the local governance of blood flow by the metabolic activities of the cells; this now stands as proved. When these metabolites overflow into the general circulation their effects are met by those of vasoconstrictor substances poured out by special glandular apparatuses. It has been suggested that a chief function of these constrictor substances is thus explained.

There is again the control, direct and indirect, through the central nervous system; the latter and the metabolic control are functionally interwoven. Thus, antidromic impulses are thought to act indirectly on the blood vessels by changing metabolism; and again, the vasodilator substances, liberated by metabolic activities or by injury, play on the strong arterioles through local nervous channels. The full interrelation between these two mechanisms still remains unrevealed. Although there are good reasons for believing that central vasoconstrictor impulses, the direct nervous influence, may proceed as far as the finest vessels; and although local metabolites may influence the arterioles through local nervous channels; yet broadly speaking the following generalisation is true.

The blood flow to the skin is regulated in a twofold manner; by the tone of arteries and strong arterioles on the one hand; by the tone of endothelial vessels on the other. The first mechanism is mainly under the governance of the central nervous system, and forms a coarse adjustment; the second is controlled more directly by the local tissue needs and forms a fine adjustment of great precision.

CHAPTER XVIII.

AN IRRESPONSIVE CONDITION OF THE MINUTE VESSELS.

Refractoriness.

IT has been related in Chapter VII how Grant and I found that, if histamine is punctured into the skin of the arm after the circulation to the limb has been arrested, if this circulatory arrest is maintained for a number of minutes, and especially if the skin is simultaneously heated, then on releasing the vessels the usual whealing fails to occur. Although in this experiment the vessels affected by histamine at first acquire during the period of arrest the usual increased permeability, it soon subsides. The decline of previously increased permeability is accompanied by another manifestation, namely, a refusal, complete or partial, of the vessels to respond to histamine reintroduced. To this state the term refractoriness, or relative refractoriness, is applied. The main observations have since been confirmed by Hare (*105*).

It was further shown that this refractoriness to histamine, itself induced by histamine, is not an isolated phenomenon. If in a case of urticaria factitia the stroked skin is similarly treated, no wheal develops and the skin may then be shown to have become refractory to histamine, to morphia, and also, although this demonstration is less easy, to further stroking. If an area of the same skin is rendered refractory by histamine, then a firm stroke carried across the area will subsequently wheal the skin except where the stroke crosses the refractory area. These observations are all similar in that whealing of the skin in response to a first stimulus is prevented by arresting the circulation until a sufficient period has elapsed to allow the increased permeability of the vessels to decline ; a second stimulus then applied fails to produce response although the circulation is released.

It was also shown that if, in a susceptible subject, the skin is actually allowed to wheal after stroking it, and a second stroke is then carried across the first wheal during its stage of subsidence, the second wheal is broken where it crosses the original one. Thus, the refractory state is not confined to skin in which the circulation has been arrested, but is manifested by the vessels affected in a stroke wheal that develops and subsides naturally. Further examples of a similar kind will now be cited. Where it is not otherwise stated they are taken from my recent report (*162*).

If the skin is frozen hard and allowed to thaw, a reaction occurs, which in its broad features is indistinguishable from that produced by histamine, or by stroking when the skin is susceptible. The skin wheals prominently,

the swelling subsides in 24 hours or more and the frozen area is left of a deep red colour. If this same area of skin is refrozen within a day or two the second reaction is limited to increased reddening, which persists, but there is little or no whealing. The experiment is most strikingly demonstrated by causing the second freeze to overlap the first ; appreciable whealing is then confined to the area of skin originally unaffected. A similar observation has been recorded by Duke (*72*). Very many of these areas, left dark red by previous freezing, have been tested with histamine, and they are always found to be more or less refractory to it. Complete failure to respond by whealing is seen when the previous freezing has been at a very low temperature (about —20°C) and has been prolonged for 15 to 20 seconds or longer. After hard and prolonged freezing the failure to respond may persist for 5 days and the response may be a reduced one for 8 or more additional days. After less severe freezing there is usually very slight whealing at first to histamine ; the response increases gradually in its degree, full wheals being obtained after the lapse of several or many days. In these instances the difference between the wheal on the frozen skin and on control skin is less conspicuous if very strong solutions (1 in 300 or 1 in 30) of histamine are used, but it is still manifest.

A patch of skin was hard frozen in a case of urticaria factitia so that it whealed subsequently. The next day a firm stroke was drawn across the skin left red by the freeze. The stroke wheal that developed was interrupted over this area.

Duke (*72*) records a curious instance of sensitiveness to cold ; exposure of the skin to water at 10 to 15°C for two minutes, was shortly followed by whealing of the treated skin. The significant observation is that the skin so reacting became " totally exhausted so that further application of cold caused no effect whatever." The period of exhaustion lasted 2 hours. This example is to be distinguished from the reaction to freezing.

I have tested the effects of burning heat on two areas of my own skin. One of these areas had been whealed by exposure to a temperature of 47 to 48·7°C for 4½ minutes, the other had been whealed and lightly blistered by exposure to a temperature rising from 47° to 52°C in 9 minutes. The first refused to wheal to histamine on the next day ; the second showed little or no whealing to histamine on the second day, when it was first tested. In both instances the skin was red but unswollen when tested.

Ultraviolet light burns behave in the same way. The skin is exposed for 4 to 8 or sometimes 15 minutes at a distance of 18 inches from a quartz mercury vapour lamp ; exposures that give deep redness of the skin with a little swelling, and usually tenderness, by the following day. Such burns usually react only just perceptibly to punctures of 1 in 3,000 and 1 in 300 histamine during the two days following irradiation, and the more severe often fail to show recognisable whealing. X ray and radium burns behave similarly. If an ultraviolet burn is frozen, the wheal that appears is lower or is absent where the frozen and irradiated areas coincide.

In an urticarial case an area of the skin of the back was irradiated.
On each of the next three days, the skin was firmly stroked, the line passing
over the patch of irradiated and reddened skin. A conspicuous wheal
formed on each occasion but was broken completely over the irradiated
area. Duke records the case of a woman who had become increasingly
sensitive to sunlight (*71, 72*). Exposure gave rise in $2\frac{1}{2}$ minutes to itching
and erythema, shortly followed by wheals. He records that areas previously
exposed refused to react again for several days.

Similarly the skin that has been deeply reddened and slightly swollen,
by applying $2\frac{1}{2}$ per cent. mustard gas oil, a condition maintained for many
days, fails at first to react to histamine, or the reaction is much reduced.

Hare (*105*) has shown that in " protein sensitivity " stimulation by
means of the appropriate antigen will render the skin refractory to histamine
or to a further dose of antigen, and that skin rendered refractory by histamine
has similar effects.

These and other examples are summed up in the accompanying table.
Ten different forms of original stimulus have been used, and these have
been found to render the skin refractory to stimuli of various kinds. Many
have been tested against a repetition of a like stimulus ; all but cold have
been tested against histamine. The results are uniform. Clearly, an almost
endless variety of combinations might be tested ; but, since experience has
shown no exceptions, the following induction seems justified. If the skin
is so damaged that it becomes red and œdematous, then, when the œdema
has subsided but deep redness persists, the skin remains for some while
refractory, in the absolute or relative sense, to a repetition of the same
stimulus, *or to any stimulus that produces a similar original lesion on control
skin.*

	Original stimulus.	Stimulus failing to re-wheal.
1.	Histamine	Histamine. Stroke. Antigen in susceptible.
2.	Stroke	Stroke. Histamine. Morphia.
3.	Freezing	Freezing. Histamine. Stroke.
4.	Cold	Cold.
5.	Burning heat	Histamine.
6.	Ultraviolet light	Histamine. Freezing. Stroke.
7.	X ray	Histamine.
8.	Radium	Histamine.
9.	Mustard gas	Histamine.
10.	Antigen in protein susceptible	Histamine. Antigen.

Incidentally, these observations form strong confirmatory evidence that the stimuli in question act through a mechanism common to all, the link between refractoriness to varying stimuli being our H-substance. But I here use them to emphasise that refractoriness seems universal when stimulation of the cutaneous vessels has been sufficiently powerful to induce a preliminary increase in the permeability of their walls.

It is to be remarked that the refractoriness now referred to is a refractoriness in a limited sense ; it concerns only increased permeability, and is intended to include neither the local dilatation of minute blood vessels, nor the surrounding arteriolar flare, which, together with increased permeability, comprise the triple response of the skin to injury.

So far as local dilatation of vessels is concerned, definite evidence is unobtainable, for dilatation is as a rule already full when the second stimulus is applied. If, as a result of the first stimulus, the skin is not fully reddened, then the second stimulus will redden it further. This is clearly to be seen when skin has been frozen or irradiated,* and when either of these stimuli is subsequently employed, but it is in these instances of incomplete reddening that refractoriness to the second stimulus is usually found to be incomplete.

So far as the flare is concerned, there is clear evidence. Thus, if histamine is punctured into an area of skin reddened by previous freezing, burning heat, irradiation or by mustard gas, locally the skin redness becomes brighter in tint and the flare appears in the surrounding normal skin. This is so whether slight whealing occurs or whether whealing fails altogether. The flare is often as widespread and vivid as on control skin ; sometimes its extent may be reduced. The only distinct exceptions to the rule have been seen when histamine has been punctured into skin reddened by very severe previous freezing, and when sensation has been partly or wholly lost in the affected skin as a result ; in these instances the flare may not be seen. Since the flare is dependent upon a local nervous reflex, these exceptions are readily explained. The flare has also been noted in the following circumstances, namely, when skin previously reddened by freezing is refrozen, when the skin irradiated to bright redness is frozen, and when a heavy stroke is carried through an area of skin reddened by freezing or by irradiation, although in each instance whealing to the second stimulus was imperceptible.

These facts are important in showing, firstly, that the nerve endings do not participate in the refractory state, and secondly, that refractoriness does not consist of a failure of the tissues to liberate our H-substance ; for the flare is due to the presence of such a body as Grant and I demonstrated (see page 88).

Nature of refractoriness. It is possible *a priori* to conceive the change involved in refractoriness as one in the cells proper to the skin, and

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* It is sometimes stated that skin reddened by irradiation is not reddened further by renewed irradiation. The statement is untrue unless the original reddening is full or unless the skin is in a pigmented state when the irradiation is repeated.

thus to regard it as due to the physiological stimulation or overstimulation of these cells; refractoriness could then be viewed as comparable to the similar phenomenon in stimulated nerve or muscle. Such a conception is placed out of court by the evidence just given and is out of harmony with the conclusion, for which there is now abundant evidence, that in physical injury H-substance is liberated in the skin. If the last conclusion and the conception now discussed were both valid, then refractoriness would be equivalent to inability of the cell to respond and release the H-substance at the second stimulus; but obviously such a view cannot be held, since the skin damaged by a first stimulus, fails to react to histamine when this is introduced from without. For these reasons I conclude that refractoriness resides not in the cell proper to the skin, but in the vessel wall, and this conclusion is supported by further observations presently to be recorded, for it can actually be shown that the vessels are in a peculiar state.

The precise meaning of refractoriness remains in doubt.* Grant and I discussed the question briefly in our paper, and considered whether the increased permeability occurring in the vessel wall might be confined to the period during which histamine, or its equivalent, is passing into the cells concerned. Such an interaction would be reminiscent of that of muscarine on heart muscle as described by Straub (*237*), who demonstrated that the muscarine effect is produced only while the poison is actually penetrating the cells, and that once saturated they refuse to respond again. In that case refractoriness while histamine remains *in situ* would be anticipated, provided the concentration of this substance in the tissues had not become appreciably lowered in the interval. This mode of action, however, seems to be denied by the observation, that when histamine has been punctured in as a first stimulus and the tissue has been rendered refractory, subsequent delayed whealing may occur although no fresh stimulus is applied (*164*).

The delay may be 15 minutes or more. It is exceptional in the case of stroke wheal, more frequent in the case of histamine wheals, and is supposedly due to the reactivity of the tissues being restored before all the histamine, or the H-substance liberated by stroking, has left the skin. If this explanation is adopted, however, Straub's muscarine experiment can scarcely be accepted as a strict analogy, since in our experiment it is necessary to assume that the circulation restores reactivity of the vessel wall cells while these are still in contact with the substances that originally rendered them refractory. When, as occasionally happens in the case of a stroke stimulus, and when, as usually happens in the case of the protein stimulus applied to sensitised skin, a delayed wheal appears after a period of refractoriness, a continued release of our H-substance may be postulated to account for the appearance of this wheal (*105*).

Attempts have been made to carry the question farther by studying the effects of repuncturing the same skin repeatedly with histamine. A strong

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* The phenomenon occurs equally well in skin to which the nerves have degenerated (*167*).

solution (1 in 300) is used and a first puncture is laid down ; this is followed by a brilliant flare and a wheal 4 to 6 mm. in diameter. The flare and wheal gradually subside ; usually there is little trace of them by the end of an hour. If histamine is now repunctured into the same point, a full reaction is again seen, flare and wheal reappearing in their original forms. In the first subject used it was found that earlier repunctures failed to produce this effect, repunctures at half hour intervals from the first giving no appreciable renewal of either wheal or flare, although the original wheal and flare had declined very greatly. It was also noted that this repuncture seemingly deferred subsequent reactivity, a third puncture yielding a response only when an hour had elapsed from the second. The observation appeared to provide some evidence in favour of the view that histamine lying *in situ* maintains refractoriness. More extended observations have failed to yield decisive results. In another subject a return of the flare and an increase of the subsiding wheal has been seen repeatedly when the repunctures have been placed at much shorter intervals ; and the same events have since been witnessed in the subject originally tested. The observations have been singularly lacking in uniformity and have thrown no further light on the question discussed.

So far as the occasional failure of the flare to return on repuncture is concerned, this is probably due in part to the development of a high tone in the minute vessels of the skin from which the previous flare has receded, for the same skin frequently fails to flush, or flushes only slightly or partially, when the new puncture is set down well away from the original site of puncture or even immediately outside the area of the previous flare. In several subjects tested, however, it has been observed that if the same spot is repunctured many times at half hour intervals, the reaction, as judged both by the wheal and flare, lessens very decidedly, until eventually repuncture is without any appreciable effect (see *248*).

Irresponsiveness to vasoconstrictor substances.

We return to the condition of the vessels in skin reddened by injury. In such skin all the minute vessels participate in the reaction. This is now known of all the stimuli referred to in this chapter. These vessels are of one class ; they are endothelial tubes and possess no coat of smooth muscle. It is also known that all these vessels, when normal, actively constrict when adrenalin or pituitary extract is applied to them.

The vessels of the skin, when dilated subsequent to injury, are found to have become temporarily irresponsive, in the absolute or relative sense, to these vasoconstrictor substances, just as they become irresponsive after experiencing histamine, introduced from without.

It is clear that histamine itself is capable of preventing or abolishing temporarily the response of the vessels to adrenalin, as the following observations show. A solution of 1 in 3,000 solution of histamine is punctured

into 4 points of the skin of the forearm to which the circulation has been arrested. The arm is then plunged into water at 44° for 6 minutes, the object of this procedure being to prevent subsequent whealing. During the 6 minutes, four purple spots appear at the sites of the punctures and grow gradually until they are of about 4 mm. diameter. While the circulation remains arrested, one of these spots is punctured with a 1 in 1,000 adrenalin solution, the control skin being similarly treated. The latter blanches in about 2 minutes, while the purple spot remains unchanged. The circulation is now released and 3 minutes later adrenalin is punctured into a second purple spot and into a control area. The latter blanches in a minute or two, the former does not. After a delay of about 7 to 10 minutes the areas into which both histamine and adrenalin have been punctured begin to blanch, as the histamine is washed away. The two remaining histamine areas present no whealing, or if repunctured with histamine, yield little or no whealing ; the vessels have entered the refractory state. This observation is more apposite to those that follow than the converse experiment, in which histamine is punctured into an area of skin already blanched by adrenalin. This procedure is followed by the appearance of a red or bluish spot in the blanched area ; histamine breaks down full adrenalin blanching completely or partially when introduced in strengths down to 1 in 300,000. A 1 in 3,000 solution produces deep redness, 1 in 30,000 bright pinkness, and 1 in 300,000 slight pinkness, in the blanched area. A simple needle prick into an area of adrenalin pallor soon becomes surrounded by a little pink zone, in which the capillaries are seen microscopically to be dilated. That is so according to our view because the injury of the prick liberates H-substance.

The corresponding phenomenon in the case of injury is most readily studied in the case of the vascular dilatation that follows severe freezing, for the dilatation is maximal and persistent. In such instances, a solution of adrenalin (1 in 1,000) punctured into the reddened area yields absolutely no visible response, unless it diffuses through the reddened skin into surrounding normal skin, which then blanches vividly. If adrenalin is punctured into normal skin near the red area, the skin blanches vividly up to but not beyond the red border. After less severe freezing it is usual to see very faint blanching to adrenalin ; after milder freezing a reduced reaction is the rule.*

The force of the contraction represented by the imperfect blanching is less than that happening in control skin. If a little additional pressure is thrown upon the veins (20, 30 or 40 mm. Hg) the faint blanching disappears ; it is often sufficient to allow the limb to hang down to abolish a slight blanching produced when the limb was horizontal. The blanching of control skin by adrenalin persists for a long while after the venous pressure is raised to a much higher level. Now if adrenalin is punctured into skin *already* congested, by throwing pressure (50, 60 or 70 mm. Hg) upon the veins, blanching

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* If the reduced blanching is watched microscopically some capillaries are seen to disappear and the subpapillary venous plexus becomes less distinct and in part vanishes. This statement is known to be true of areas that have been frozen or reddened by ultraviolet light.

is imperfect, and it may be argued that the failure of the vessels to respond in the reddened (injured) area is due, not to a condition of the vessel wall, but to increased pressure within the minute vessels, the contraction being thus resisted. This is not the case, for if adrenalin is punctured into skin reddened reflexly, as in the flare surrounding a wheal, the blanching that follows is intense, and it is as difficult to dilate the closed vessels by increasing venous pressure, as it is to dilate vessels similarly blanched in skin previously unflushed. Again, the skin reddened by injury is equally irresponsive to adrenalin if the circulation to the limb has been first arrested, without allowing much blood to stand in the veins ; this is so although the arrest of the blood flow soon reduces the pressure in all the minute vessels almost to uniformity. It is also clear from the same experiment that failure to blanch, or reduced blanching, is not due to the adrenalin being removed more quickly from the reddened skin. The failure of blanching is not attributable to distention of the vessels tested, for pressure exerted from without after the stimulus is laid down empties the vessels ; they refill, although surrounded by adrenalin, as soon as the pressure is withdrawn. Their walls are incapable of contracting in response to adrenalin or are capable only of imperfect contraction.

Statements exactly similar in every respect to those made for adrenalin are true of pituitary extract.

These observations upon the skin reddened by freezing have been repeated upon skin that has previously been whealed a day or so before by burning heat, or that has been reddened by ultraviolet light or by the application of mustard gas. It is insufficient to render the skin pink by the last methods, it must be deeply reddened and must have been slightly or distinctly whealed. The reactions to adrenalin and pituitary extract are deficient in precisely the same respects as are those upon areas reddened by previous freezing.

Nature of irresponsiveness. We have now seen that the vessels of the injured skin fail to show their whealing reactions to histamine, or to equivalent substances liberated by reinjury, on the one hand, and to vasoconstrictor substances on the other. These two associated phenomena are not necessarily due to one and the same ultimate vascular defect. There is some evidence that the defect may not be a single one. Thus, it is impossible accurately to predict from a complete absence of histamine whealing that adrenalin will completely fail to blanch, or *vice versa* ; though when one reaction has been much reduced the other always has been in the observations so far recorded. In a curious case of pathological œdema of the skin, in which little reddening was present, considerable refractoriness was found at the subsidence of the œdema, but adrenalin blanched the skin fully (*174*).

The defective reaction of the vessels of the injured skin to adrenalin and to pituitary extracts after injuries of various kinds, or after a histamine application, may be regarded as showing that these vessels are dilated because they have lost their power to contract to normal stimuli, and to this their original dilatation and its maintenance may be attributed. The precise manner

in which this is brought about, and the reason why the vessels sometimes recover slowly (after freezing) and sometimes more quickly (after irradiation and particularly after mechanical injury) are open to question ; but interesting questions are raised, which may be discussed briefly. One of two views may be held.

The first view is that at the time of the injury the contractile mechanism is abruptly thrown out of gear and that this condition is more or less persistent. Stated in this form the hypothesis is incomplete, for histamine or its equivalent must be introduced as the original cause of the vascular state. The hypothesis seems to require that, in acting originally, a histamine like body binds on to the contractile cells of the vessel wall and that the breaking down of this combination and the recovery of normal metabolism is slowly accomplished.

The second view supposes similarly that the adrenalin and pituitary reactions fail because the vessels are held dilated by histamine or its equivalent, but that this substance forms a less stable union with the cell, being constantly renewed over a lesser or greater interval of time.

Now the local reddening caused when histamine is itself introduced is of relatively brief duration and the H-substance, released by injury, is known to diffuse at much the same rate. It is difficult to suppose, therefore, that the contractile cells of the vessel wall can hold histamine or H-substance in combination for long periods, or that the vessel wall can long remain in contact with such bodies unless these are replaced. This argument favours the second rather than the first hypothesis.

Be the ultimate cause of the vascular condition, summed up in the two terms, irresponsiveness and refractoriness, what it may, the state is a well defined and important one. It is a condition in which the minute vessels of the skin are dilated, and in which they refuse on the one hand to respond fully or at all to vasoconstrictor substances, or on the other to respond fully or at all to histamine, or equivalent substances, in so far as these cause increased permeability.

A similar state of the vessels exists in certain pathological conditions and in normal skin that is highly coloured, as will be described in the next chapter.

CHAPTER XIX.

LOCAL VARIATIONS OF SKIN COLOUR AND OF MINUTE VESSEL TONE.

Number and size of vessels related to skin colour.

It is familiar knowledge that certain parts of the skin are more highly coloured by the blood within their vessels than are others. The reddest parts are the skin of the face, of the palms and backs of the hands, of the soles of the feet and, less conspicuously, of the buttocks. In the face, it is the cheeks and lobes of the ears that are in general most highly tinted, though in different individuals there is much variation. The reasons for these differences in colour are beginning to be understood ; there are related problems deserving attention and the chief of these I propose to discuss in the present chapter.

It will be evident upon reflection that those parts of the skin are most highly coloured, which are either unclothed by the fashion of our times and are as a consequence most frequently exposed to light, wind and change of temperature, or which are oftenest submitted to pressure, tension, and friction. The first factors influence the skin of face and hands, less generally and to varying extent that of neck, chest, arms and legs. The second factors influence the palms of the hands and soles of the feet, the buttocks and the skin covering extensor surfaces of joints.

The palms of the hands, the soles of the feet, and in much smaller degree the buttocks, are from birth endowed with unusually rich meshworks of cutaneous vessels (231); a greater vascularity that helps to provide for the pressure and rough usage subsequently experienced. The capillaries and meshworks of minute vessels are most closely set in skin that is ridged.

If counts are made of the capillaries in unridged skin in different regions that vary in relative redness, complete uniformity is not found. Thus Wetzel and Zotterman, (263) who at my suggestion have taken up this question in the living subject, find on comparing the skin of the back of the hand and arm, that the former presents somewhat more closely set capillaries ; but the knuckles, which are commonly redder than the back of the hand, are no more than equally supplied by capillaries. Full counts of the capillaries in the lobe of the ear, the cheeks, and in circumoral skin similarly fail to show any fixed relation between numbers of vessels and depth of skin colour. In

Fig. 72.   From Wetzel and Zotterman's paper.   Typical views of the minute
         vessels of the skin in the living subject.   A, B, and C, taken from the
         blistered skin of a normal lad of 16 years, illustrate the forearm, the
         back of the hand, and the knuckle respectively, these three areas of
         skin presenting increasing depth of colour in this order.   D, E, and F,
         from normal unmolested skins.   D, from the pale circumoral skin of
         a male subject of 29 years.   E, from the highly coloured cheek of a
         lad of 12 years.   F, from the red helix of the ear of a lad of 15 years.
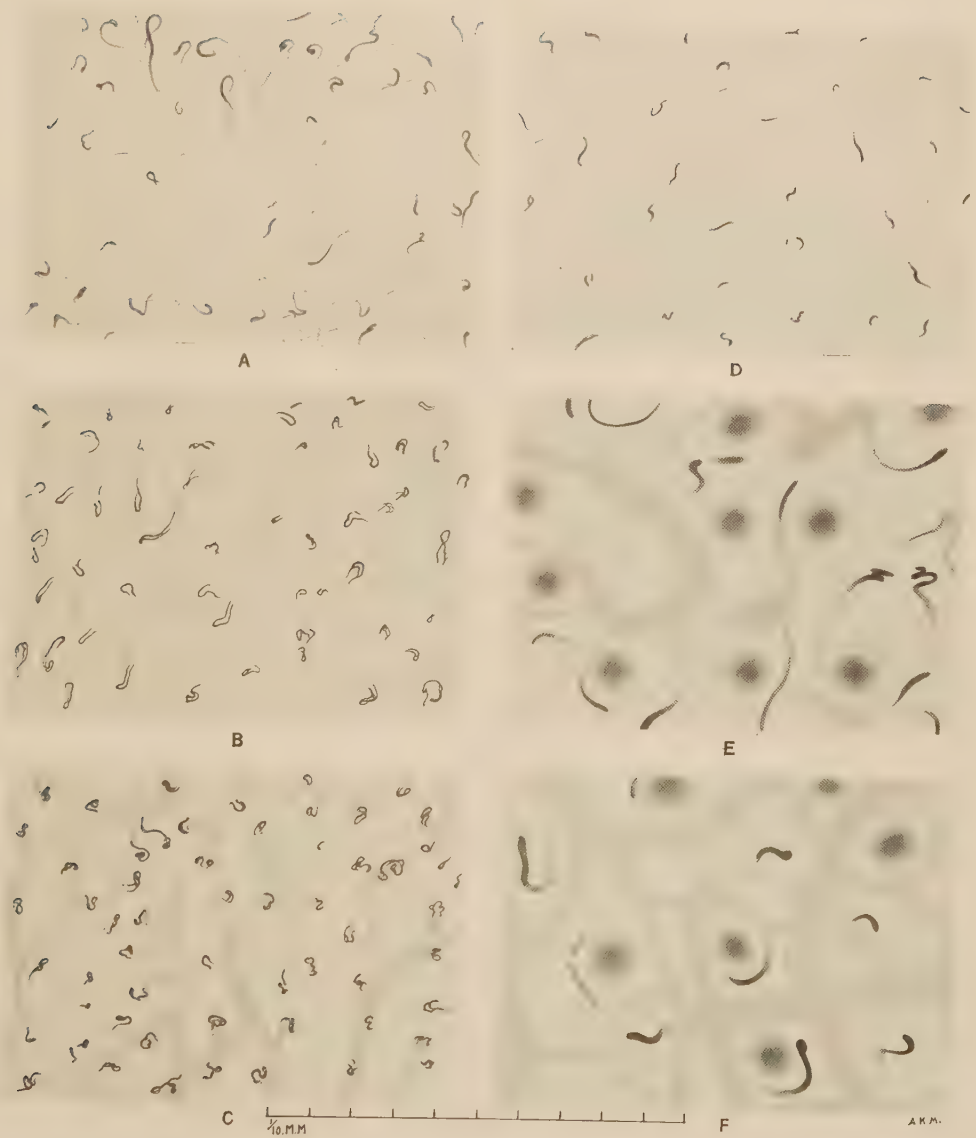
Fig. 72.

the accompanying table the numbers of capillaries to a square millimetre of skin in these different parts are indicated by average values.

Skin area.	Capillaries to sq. mm.
Knuckles	58
Dorsum of hand	65
Forearm	47
Cheek	16
Lobe of ear	38
Circumoral skin	20

This enumeration of capillaries has not for its purpose a calculation of the extent to which capillaries in various parts directly contribute to skin colour ; for it is already known that in most regions the capillaries contribute little (see page 17). The object is to obtain from such counts an expression of the density of the meshworks of fine vessels from which they spring and particularly into which they pour ; for in general, the closer set the capillaries, the closer set are the meshes of the minute vessels with which they connect. Such observations, combined with others upon comparative depths of tint in the respective parts, at once render it evident that between the two there is for the most part no distinct relation.

In these observations of different areas, the relative sizes of the vessels, both capillaries and minute venules, can be ascertained by inspection and, in this respect, the relation to depth of tint is usually notable. Thus, when the knuckle, back of hand and arm present a range of colour intensity, in this order from the deep to the less deep, it is to be seen that the sizes of the capillaries and of those portions of the venules that may be rendered visible present a similar order (Fig. 72, page 251). It is very noticeably so also in the case of the face. In the red cheek and in the red lobe of the ear the numbers of capillaries are no greater than in the pale circumoral skin, but the sizes of the vessels, especially of the venules, differ remarkably. In the circumoral skin these vessels when visible are of similar size to those found in the forearm and trunk ; in the lobe of the ear and cheek they are very much larger (Fig. 72). In the pink or red cheek the venules are of such magnitude that they are not infrequently distinctly perceptible to the naked eye both in children and in adults ; that is to say they are about 0·2 mm. or a little more in diameter. As age advances, their prominence often increases so far that they constitute meshworks that the unaided sight can trace out in detail at a considerable distance from the subject who displays them ; individually they are often of a half millimetre in diameter, and not infrequently exceed this measure. In the skin of limbs and trunk the venule diameters are usually about 0·015 to 0·02 mm.

The grossly enlarged venules of the face though most commonly found upon the cheeks, are also frequent on the nose, and there is no part of the face in which they may not develop. Age* and exposure are chiefly to be associated with their prominence. Grossly enlarged venules may be pathological in the sense that they are not usual or proper to the skin of children, but almost all adults present venules that are visible, and there are few children of 5 years or more in whom some are not discernible with the naked eye.

It is difficult to speak of such a state as abnormal, a state which seems to come in all those who, of intent or otherwise, have not hesitated to hold their faces to the sun, or to buffet with the winds. The forethought of some, the less deliberate act of other dwellers in the cities, may preserve in facial skin a youthfully smooth and pallid tint; the fact that fashion, here

Contribution of capillaries and venules to skin colour (after Wetzel and Zotterman).

Region.	Diameters in μ		Surface area of vessels per sq. mm. of skin.				Prevailing colour.
	Capillaries.	venules.	Total.	capillaries.	venules.	Percentage of venules to total.	
			mm²	mm²	mm²		
Knuckle	15	32	0·177	0·039	0·138	78	Red.
Hand	10	25	0·125	0·020	0·105	84	Pink.
Arm	7	17	0·087	0·007	0·080	92	Pale.
Cheek	19	63	0·207	0·010	0·197	95	Deep red.
Lobe of ear	11	37	0·126	0·008	0·118	94	
Circumoral skin.	7	15	0·035	0·003	0·032	91	Pale.

more persistent than is its custom, continues thus to define "complexion", may not change our view of normal coloration. From this standpoint, the venules of the weather beaten skin, be it of the face or of the hand, for the latter less often shows a conspicuous change, are physiological, and as such I here consider them. If we exclude instances of distinct telangiectases,† the average contribution of the superficial vessels to skin colour may be summed up as has been done by Wetzel and Zotterman in the accompanying table.

The depth of skin colour in various regions of the body may be influenced here and there, as in the palm of the hand, by original vascularity; the dominant influence is size of venule.

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* The number of capillaries to the square millimetre does not seem to change appreciably from youth to old age (*263*).

† Here meaning diffuse collections of venules that are very readily visible.

The condition of the dilated venules.

Recent observations that I have undertaken (*162*) help to explain the widening of the venules just discussed. Their dimensions are due to decreased tone, whereby they offer smaller resistance to transmitted arteriolar pressure. Unlike the normal venules of the skin, grossly dilated venules of the face fail to respond, wholly as a rule, to vasoconstrictor substances. If a needle point is lightly driven into skin through drops of 1 in 1,000 adrenalin, and the punctures are placed close to, and one on either side of, a large facial venule, the skin blanches vividly, but the venule does not contract ; it is left as an unchanged or almost unchanged red strand crossing on a pale background. A similar result is to be obtained with pituitary extracts (*162*).

If, after puncturing in adrenalin, the vessel is pressed upon and emptied until blanching has had time to develop, the release of external pressure is followed by filling of the vessel tested ; now normal venules of equal size, which can be seen lying deeply in transparent skin, react well to adrenalin. For these and other reasons I conclude that the failure on the part of the facial venules to contract is due to loss of contractile power, and not to increased pressure within them, nor to the distension of the walls, a distension that would place the contractile elements at a mechanical disadvantage.

The venules may have become dilated more locally and are then more decidedly pathological ; forming small circular or spider shaped collections of vessels in the skin, also termed telangiectases. I have investigated many of them (*162*) and they similarly fail to react ; because these are frankly pathological, they will not be considered at length, but their origin and behaviour strongly supports the views here expressed.

The diffuse and visible facial venules fail, as stated, to react to adrenalin, but the background colour, coming from venules of a smaller order, is lost. The contractile force that the last vessels can exert may be tested in the following way. When vivid blanching of the background colour has been induced by adrenalin, a glass covered capsule is applied to the skin, and the suction force required to flush this pallid zone is taken as a measure. This method has been used to test many instances of reddened facial skin, and it is found that a very slight negative pressure suffices for this purpose. Usually, the simple act of placing the capsule against the skin, with sufficient pressure just to seal its mouth, congests the skin enough to abolish the adrenalin pallor. On the trunk and limbs, similarly blanched areas resist suction of—80 mm. Hg, and more, before they vanish.

Wetzel and Zotterman (*263*) have since used these tests more extensively and find that the contractile force exerted by the vessels varies in different subjects and in different regions of the face. On the cheeks and ears it is in general least, on the circumoral region it is greatest ; original pallor or original high colouring, whether the venules are grossly distended or not, are almost always found to be associated with high and low minute vessel tone, respectively.

In the case of the limbs, the tone is tested more conveniently by imposing pressure on the veins. If an arm is chosen in which the skin colour is well graded, knuckles red, arm itself pale, and the back of the hand intermediate, the adrenalin reactions in these three situations vary inversely as their brightness, the knuckles showing least and the arm most pallor ; and the blanching on the arm withstands heavy venous pressure, while that on the knuckle withstands little (*162, 263*).

It is concluded, therefore, that in regions of skin that are red because the venules are dilated, these dilatations are due to inability of the vessels to display full tone.

In the last chapter it has been seen that continued redness of the skin in response to deliberate injury, such as freezing, ultraviolet and radium emanations is similar in nature ; the vessels lose, partially or altogether, their power to react to adrenalin and to pituitary extract. This irresponsiveness is associated in each instance with refractoriness, partial or complete, to histamine. Similarly in the reddened skin of the face or hand now discussed, the histamine reaction is reduced in extent ; this is most noticeable in the case of those local telangiectatic collections to which I have referred (*162*).

When skin has shown prolonged reddening as a result of injury, such as that produced by ultraviolet light, by X ray application, or by radium burns, the subsequent development of grossly distended superficial vessels is not an infrequent sequel ; it was in large part with such telangiectases that I dealt in my original article (*162*).

When the series of facts now set forth is considered as a whole, the meaning of the more striking regional differences of skin colour begins to become clear. There are areas particularly exposed to influences, such as sunlight, that are known to induce relative irresponsiveness of the minute vessels. The vessels under these influences lose tone and dilate, and the skin assumes its habitual heightened colour.

The peculiar distribution of dilated vessels in the face still remains to be discussed ; although this must be acknowledged to be variable, it is customary for the circumoral and circumorbital skin to be remarkably free from dilated venules, the skin along the margin of the lower jaw and over the chin is less exempt. The brightest colour is found in what may be termed the malar triangle, the apex of which is at or upon the nose and the broad and less defined base of which lies beyond the cheek ; the upper arm and lower borders of the triangle are often almost straightly linear, the upper lying below the orbit, the lower just without the nasolabial fold. The usual absence of dilated vessels from the circumorbital and circumoral skin has not as yet found full explanation ; they are the parts of the facial skin that remain warmest in cold weather or are least exposed to sunlight.

The views here expressed, in relation to varying tone of the minute vessels, may be illustrated and applied in a number of other directions.

Thus Finsen (*84*) and also Möller (*192*) noticed that when skin has been injured by ultraviolet light and has resumed a normal appearance, it reddens

in response to friction more conspicuously than surrounding skin. Similarly I have frequently noticed that after the skin has been reddened by freezing, ultraviolet light and other forms of injury, and weeks after these marks have been lost, they will sometimes reappear faintly when pressure is thrown upon and congests the veins or in the fading of a reactive hyperæmia. When parts of the skin of the face are relatively high coloured, this coloration is greatly intensified by almost any cause that ordinarily reddens the skin, such as exposure to heat. In children who are febrile the face flushes, but it flushes peculiarly, the skin around eyes and mouth often remaining conspicuously pale by contrast. The circumoral pallor in scarlet fever was long regarded as an important sign of the disease.

Emotional blushing.

In an earlier chapter it is concluded that the tone of the minute vessels restricts the area of the reflex flare appearing after histamine is introduced

Fig. 73. Diagram showing the distribution of the blush described in the text. Curiously a small circular spot in the middle line of the chest remained unflushed. The average temperatures of the points indicated were :—$a = 33\cdot4°$; $b = 35\cdot0°$; $c = 34\cdot1°$; $d = 35\cdot7°$; $e = 34\cdot2°$; $f = 33\cdot4°$; and $g = 33\cdot7°$.

into the skin; and it has been shown that this flare may appear in such distant and isolated parts of the skin as have suffered previous damage. All these examples are similar in kind; they illustrate that differences of minute vessel tone may be concealed until enough strain is thrown upon them.

Comparable with the examples just discussed is the regional control exerted by the minute vessels upon the emotional flush. In women who blush frequently and vividly, I have noticed that the flush spreads over face

and neck and involves precisely the V-shaped area, already suffused or pigmented, that is consequent upon exposure of the lower neck and upper chest to sunlight by the cut of modern dress. The area of the blush in one such case is represented in Fig. 73 by the shading. This flush was unusually persistent and the temperatures of the reddened and surrounding skin were compared in many readings. The temperature of the former averaged 34·8° and of the latter 33·8°, as shown in the illustration and its description. In observations in my laboratory Harmer and Harris (*106, 170*) have seen the vivid flush of the face in response to a small subcutaneous dose of histamine similarly delineated on more than one occasion, and I can say the same of the amyl nitrite reaction, the flush of which has been recognised, since Aldridge's observations (*3*) were made, to affect the face and neck chiefly and to follow closely that of blushing.

The reason why the emotional blush is generally limited to the face and neck was discussed as early as 1839 by Burgess (*36*). He believed that this is in part brought about by the anatomical arrangement of the facial vessels, the path being more open to an ingress of blood. He also states that the constant passage of blood to the face, consequent on exposure to atmospheric conditions, renders the minute arterial tubes more dilatable.

His views were later overshadowed by those of Charles Darwin (*60*), who, while freely discussing those of Burgess, believed that the blush is confined to the face owing to a special governance of these vessels by the central nervous system, consequent, according to his hypothesis, upon the face being subjected to much closer and more earnest self attention than any other part of the body.

The nervous channels thought to be involved in blushing have been discussed briefly on page 207, but the facts at our disposal throw little light from this source upon the limitation of the blush. Darwin's argument revolved largely around mental concentration upon certain parts of the skin, and he points out that though exposed, the skin of the hands is rarely affected. The flush, as he remarks, is less confined in races that wear little clothing, and here it is thought that the face fails to attract undivided attention ; it is equally arguable that in these instances the vessels in other regions have been affected by atmospheric conditions, as is the facial skin in Europeans. The usual and apparent immunity of the trunk may not be found to receive its full explanation on the lines laid down, though the observations here recorded do show, as Burgess suspected, that the condition of the facial vessels may influence, and conspicuously, the distribution of the emotional blush and the visibility of the vasodilatation.

The argument may be clarified if we take a hypothetical case. In one emotional condition, that of excitation, it has been supposed that a release of adrenalin into the general circulation accounts for the symptoms of that state. In certain respects the emotional disturbance underlying blushing is of a reverse kind. If we were to imagine that H-substance is released into the general circulation by the emotional state that precedes blushing, such

release would similarly account for the symptoms of this second state. The face would blush in a manner indistinguishable from what we see, and vasodilatation in the vessels of the limbs would remain concealed from our vision, or would be revealed only by the most minute attention. The idea is purely hypothetical and has little enough to support it, but it will serve the present purpose if it emphasises that the direct intervention of efferent nervous impulses in emotional blushing is equally unproved, since blushing of the same character may be induced by means that do not involve the corresponding nervous tracts. It is clearly desirable that we should obtain more definite evidence, than we now possess, that the blush is transmitted through the cervical sympathetic nerve chain, and that we should know if in the emotional change, the temperature of the skin in general rises. In this connection it may be remembered that Darwin remarks it as curious that, when the face and neck redden, the whole surface of the body tingles and feels hot to the subject.

It is to be noted that in the face itself the *atonic* areas, as I term them, are not constant in outline and, as Campbell's careful studies (*39*) reveal, the blush affects from its start different areas in different people, just as it affects a lesser or greater part of the neck and of the chest. The degree of correlation between these varying atonic areas and those of the emotional blush in the same individuals is unknown at present.

Nature of mottled skin.

Speckling of the hands and mottling of the skin of the limbs has been dealt with in earlier chapters from certain points of view. Quite commonly both are conspicuous. The condition on the limbs is often termed marbled skin, and this is probably always present in some degree, though varying much in prominence in different individuals and in different regions of the skin examined. Inconspicuous mottling is certainly normal. I have observed conspicuous mottling often in quite young children and in all decades up to old age; it may be seen at natural skin temperatures ranging completely from 22·5° to 32·0°C. It is not abolished by immersions for 5 minutes in water ranging from 15° to 35°C, but lessens in distinctness above 40°C. The legs and arms show it most conspicuously, and in cold weather barelegged children display it clearly more often than not. It is seen best in skin that has been reddened by prolonged cooling. No part of the skin is exempt, frequently the whole body with the exception of the face is mottled. Mottling of the face, when it occurs, has a pattern similar to that on the body, but I have seen it only in quite young children.

There is little reason to doubt that the fine speckles on the hand and the larger mottlings on the limb are essentially similar in nature, for they behave alike in all conditions under which they have been tested. As the areas that comprise the mottling are relatively constant in form and in position in any given subject, they must depend upon the arrangement of some structures (vessels or nerves) in the skin ; they represent anatomical areas in the skin

(*2, 161, 215*).   The same conclusion is strongly suggested by the similarity of the pattern in form and size in different individuals.   The vessels and nerves in the palm of the hand are closer set than in the skin of limb or trunk ; and this adequately accounts for the only known difference, namely the dimensional one, between the speckling of the hand and the mottling of the paler skin (*161*).   The paler areas are enclosed by an irregular reticulation of darker zones (Fig. 74, page 263, Figs. 59 and 60, page 191).

The paleness of the enclosed area is not due to differences in the number of its vessels ; I have often counted the capillaries in adjacent pale and dark zones to find that they are equal in number, and that the arrangement and number of venules is the same in both.   Moreover, the mottling can be abolished completely by soaking the skin in stinging hot water, the vessels of the skin then becoming uniformly turgid.   The difference in the depth of colour is due to difference in the size of the vessels, and this is explained by differences in tone.   In the pale areas, tone is considerable ; these areas withstand very considerable venous pressures before they suffuse ; their conspicuousness is heightened by moderately increased venous pressure. A pressure of 70 mm. Hg fails to abolish the mottling of the arm or the speckling of the hand, and if, while the venous pressure is high or while the circulation to the limb is stopped, an area is blanched by transient external pressure, the pattern returns when the skin is released (*161*).   The white areas often resist invasion by the spreading histamine flare, as has been seen ; they sometimes resist the flush of a reactive hyperæmia, providing circulatory arrest has not been of too great duration, and has led thus to complete relaxation of the minute vessels.

The phenomenon is independent of nervous influences, general and local ; Ebbecke (*75*) states incidentally that it is independent of central nervous influences since he has seen it on the hand to which sensory and motor nerves were paralysed, and recently instances of old standing degeneration of the ulnar or median nerve have been reported from my laboratory (*167*) in which speckling was conspicuous and equal in the insensitive and sensitive skin of the fingers.   The anatomical areas above referred to would seem to correspond, therefore, to arteriolar territories.   This suggestion of regional blood flow has indeed been put forward in an explicit form by Renaut and Adamson (*see 2, 215*).

In early anatomical descriptions, funnel shaped prolongations of the connective tissue of the skin are stated to penetrate the subcutaneous fat, dividing it into compartments that have been called the fibrous cones of the skin (*215*).   These cones are supposed to influence the distribution of blood to the skin, constituting in it vascular territories, and this arrangement is thought to account for mottling, the pale areas corresponding to the centres of maximal supply and the darker reticulations, which enclose these, corresponding to the regions of marginal anastomosis and relative stagnation. Renaut states that, when skin is injected, the injection fluid first appears at these centres and spreads to become confluent.   Spread consistent with

this idea I have not seen while injecting skins, neither have I been able to detect it by the following method of natural injection. Conspicuous mottling of the skin is mapped out on the surface with ink, and the arm is depleted of blood by means of an Esmarch's bandage ; an armlet is placed around the ending of the bandage on the upper arm, the pressure is raised in it to 200 mm. Hg, and the bandage is removed. The armlet pressure is now reduced so that it lies but a few millimetres below systolic blood pressure, and blood is allowed to pass slowly into the pallid skin. It seems to appear simultaneously in the paler and darker areas of the originally mottled skin.

These observations do not necessarily conflict with the particular hypothesis put forward, though I am disinclined to accept it until more substantial evidence of its truth is forthcoming ; more particularly because it takes no account of the arterial plexuses of the skin. It seems desirable that it should be shown that there is, or is not, an exact geographical relation between the areas of mottling and the cones of the skin described.

If this or any other anatomical basis is adopted to explain mottling, it must at the same time explain the differences in the tone of the minute vessels, and here it may be said that on general principles a heightened tone is to be anticipated in areas to which the blood flows most freely, since increased flow brings into play the balancing action of the minute vessels that has been described previously (page 200).

Actually in cases of conspicuous mottling, I have been unable in repeated observations to detect anything but negligible and inconstant differences in the temperatures of redder and paler areas, and venous congestion tests also fail to decide through which the blood flows the faster ; this is no more than is to be expected if the differences in flow are slight.

Evidence drawn from extreme instances is sometimes of value, and the following case is of interest from this and other standpoints (*162*). It is an instance of what has been termed *erythema ab igne* and is produced, as has been shown conclusively (*see* Adamson *2*, Lehner and Kenedy *151*, *152*, and previous workers cited by them), by prolonged exposure to heat. The example is that of a young girl who, wearing transparent stockings, sat long and often close over a fire, developing as a consequence the deep cutaneous mottling shown in Fig. 75, page 263. The dark reticulations were of the well recognised type, being very vascular and also pigmented. These reticulations continued posteriorly into the less conspicuous network of skin marbled in the ordinary way and little exposed to heat ; this transition is usual, as Lehner and Kenedy and others have shown. The discoloration in this skin may be regarded therefore as an extreme development of marbling. The following facts, therefore, become of interest. The *average* of a large number of readings from the dark and pale areas placed the temperature of the latter 0·08°C higher than the former, indicating if anything a slightly greater blood flow through the pale areas. Of further interest and more importance, however, was the finding that the red areas failed to blanch to adrenalin, and yielded reduced wheals to histamine. It happened that this patient also manifested

Fig. 74.   *Mottling.*   A boy's leg, presenting conspicuous mottling of colour
        in cold weather.

Fig. 75.   *Erythema ab igne.*   The leg of a girl, who sat long and frequently
        in front of a fire while wearing thin stockings.   The reticular markings
        are formed by deeply congested, and pigmented, skin.
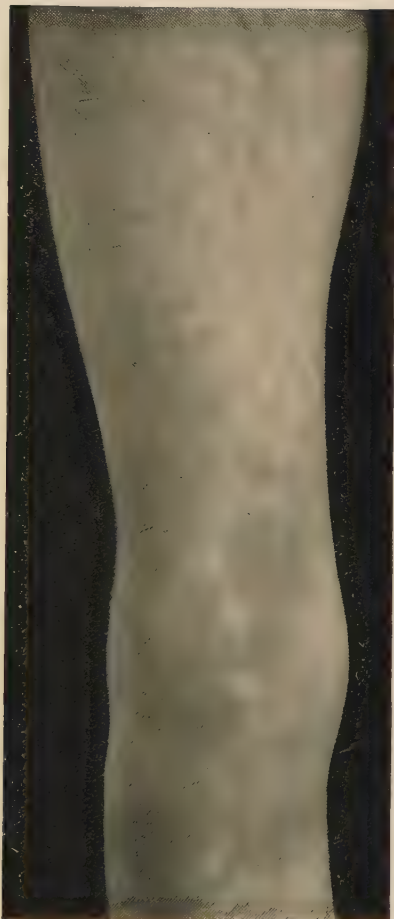
Fig. 74.

Fig. 75.

wheals to firm stroking ; such a wheal, raised on the shin, was interrupted or depressed wherever it crossed a red reticulation. Thus, it could be shown in this instance that the vessels of the dark reticulations were in the peculiar state now familiar to us, being irresponsive to adrenalin, and being refractory to histamine or the H-substance released by injury.

The question at once arose as to whether or not similar tendencies could be traced in unpigmented and less extreme instances of mottling. This has proved to be the case in respect of adrenalin, though naturally the tests are far less striking than in the instance just recorded. The blanching of the darker areas is often distinctly less complete than is that of adjacent pale areas, and the blanching in the former decidedly less resistant to increased venous pressure, and to suction applied externally (unpublished observations). This relatively low tone, previously described in the darker zones of the mottled skin, is to be connected, as in the case of the facial skin, with the peculiar condition of the walls of the minute vessels, which has been termed irresponsiveness.

If we look at the evidence collectively it points to a correspondence between areas of mottling and main arteriolar territories, the maximal points of supply being in the centre of the paler areas. This excess of blood flow, slight as it may be, would explain an associated increase of minute vessel tone and pallor. Given that the marginal areas are areas to which blood flow is slightly less, then they would be more susceptible to damage, and here the tone of the vessels, originally low, would tend to become more or less permanently inefficient, leading to quite distinct changes in responsiveness, changes that might even become associated with refractoriness as previously defined.

CHAPTER XX.

PULSATION OF SKIN COLOUR.

The association of certain signs with disease.

Visible pulsation in the human skin was first described by Quincke (*209*) and has since come to be associated most definitely with leakage of the aortic valves. It is one of many natural phenomena that, being at the time unknown to or unstressed by physiology, and being noted emphatically in disease, came to be regarded as essentially morbid. It would be easy to draw up an imposing list further illustrating this statement. For the most part such phenomena appear in a more or less limited number of healthy people or in special physiological circumstances. Thus, the "extensor response" in infants and the conspicuous respiratory irregularity of the heart in children are normal, though they have not always been so regarded. The red line bordered by white (Fig. 9, page 27), which is the normal reaction of the healthy young skin to stroking, has in times not so long past assumed and held the significant name "tâche cérébrale", being considered to denote a disorder of the brain or its membranes. Whealing of the skin in response to heavy strokes has been correlated with distinct maladies surprising and illuminating in their number. Systolic murmurs are often to be heard over hearts beating rapidly from any cause, but, being unrecognised as normal in this circumstance, they have exercised for very many years an extremely baneful influence upon certain branches of medical practice. The "pulsus paradoxus" as originally defined is in man the usual and physiological change of blood pressure with breathing, namely, a fall during inspiration and a rise during expiration. It was termed paradoxical when discovered in cases of disease of the pericardium, because a reverse relation had been described from Ludwig's laboratory as that normally prevailing in the dog.

These and similar blunders, many of which have influenced medical practice seriously and unfavourably, happened because the phenomena exhibited by healthy human beings had been studied insufficiently; a faulty habit of mind, content to associate symptoms and signs with particular diseases, without further attempting to analyse causation, has been responsible, in large part but not wholly, for this neglect. The clinician who sees for the first time a phenomenon, hitherto unknown or departing from what is regarded contemporarily as a physiological reaction, assumes, perhaps unwisely though naturally, that this phenomenon is related to

perverted function. A belated comparison of diseased subjects with controls, in sufficient number and under varying physiological conditions, eventually brings us more correctly to interpret the manifestations in question.

Many such mistakes, some trivial and some grievous in their effects, would not occur, nor occurring would they remain, as some of them do for long periods, a part of current medical teaching, if human physiology figured more prominently in the education of medical men. The medical student does not learn, or learn sufficiently, that animal physiology, and animal pharmacology too for that matter, are not in every direction precise bases on which to found the Science of Medicine.

Capillary pulsation caused by vasodilation.

" Capillary pulsation," as the term is used clinically, means that the colour of the skin varies in intensity rhythmically with the heart beat. The colour momentarily deepens with each thrust of the pulse, it pales between the pulse beats.

It may not be quite true to state that this capillary pulsation is today regarded as a positive indication of reflux at the aortic valves ; the idea that it may be connected with vascular dilatation has also been discussed on many occasions (*95, 114, 160*) since the time of Claude Bernard. Nevertheless it is certainly true to state that this correlation between a phenomenon exhibited by skin or mucous membrane on the one hand and a defective valve on the other, is the only clear impression in respect of the sign, which is today held by the great majority of medical men. Yet this common correlation is inaccurate ; even in disease of the aortic valves the pulsation is much more dependent upon a strictly local condition of the blood vessels than upon change in the general arterial blood pressures arising out of the valve injury. In aortic regurgitation, although high pulse pressure often prevails, it has been demonstrated that this is not responsible for, though it may enhance, capillary pulsation (*160*).

This conclusion was first suggested by observations on subjects in whom the femoral artery and its accompanying vein had been anastomosed by bullet wounds (*163*), the intercommunication being free. Just as a leak from the aorta to the left ventricle is followed by high pulse pressure and the water-hammer pulse, so it is in these cases of leakage from a large artery to a large vein ; these subjects also present conspicuous capillary pulsation. By obliterating the femoral artery on the proximal side of the anastomosis, the leak can be stopped and the normal pressure can be restored at will ; but this restoration of pulse pressure does not diminish the intensity of the capillary pulsation.

The phenomenon is a normal one. In young and healthy subjects lying at rest in warm rooms (20° to 22°C), it is customary to find capillary pulsation in the skin of the cheeks and in the mucous membrane of the lips. It is not often obvious though it may be definite in the untouched skin ; usually it is displayed by laying a glass slide on the skin, exerting a little pressure,

so that a central area is rendered pale; the line of junction between the suffused and pallid skin pulsates to and fro with each beat of the heart. It is also frequent in the skin on the ventral surface of the hands and fingers and in the corresponding skin of the feet. Thus it is most prominent in skin that is richly supplied by blood vessels, though there is no part of the integument which may not display it. It is seen in children and in young adults much more often than in the elderly.

Its relation to vasodilatation was indicated very early by Quincke (*209*), who saw it in skin flushed by fever. Inhalation of amyl nitrite, which flushes and warms the face, causes pulsation to become visible or to be exaggerated in this skin. A similar statement applies to the emotional blush, which floods the same skin and raises its temperature 1° or 2°C. Capillary pulsation occurs in many conditions of sickness; in these vasodilatation is prominent and the skin is hot; the association is notable in exophthalmic goitre (*95*) and, as has recently been shown, in aortic regurgitation itself. In free aortic regurgitation and in cases of arteriovenous aneurism, the facial skin is particularly affected, and its temperature is higher than that of controls, examined in similar circumstances of rest and room temperature (*160*).

The relation of pulsation to skin temperature is a very close one, and is illustrated most convincingly in different skin areas of one and the same subject. The accompanying table summarises observations upon a subject

Pulsation in areas of different temperature (Rectal temp. 37·6°C).

Area examined.	Capillary pulse.	Temp.
Lobe of right ear ...	none	23·4°C
Bed of finger nail ...	none	26·8°
Side of nose	none	26·8°
Pad of finger	none	28·1°
Pad of big toe	none	28·1°
Heel...	none	28·5°
Right cheek	slight	28·9°
Pad of big toe after massage	distinct	31·2°
Forehead ...	very distinct (spontaneous)	32·0°
Left cheek	very distinct (spontaneous)	32·6°
Right cheek (later)	very distinct (spontaneous)	33·6°
Lower lip, facial mucous membrane	vivid	34·7°
Lobe of right ear after massage ...	vivid	35·5°

displaying it and shows clearly how visible pulsation is related in its degree to warmth of the skin. In aortic regurgitation capillary pulsation is rarely seen in skin if the temperature is below 28°C, slight pulsation is usually found when the temperature lies between 28° and 30°C; it is distinct between temperatures of 31° and 33°C, and becomes vivid when the skin registers 33° to 35°C. In normal subjects the scale of temperatures for corresponding grades of pulsation is similar, but ranges higher, and the vivid pulsation **of free aortic regurgitation is not often seen.**

A further and instructive example is that of an instance of left cervical sympathetic palsy, consequent upon pressure of an aneurism upon this system of nerves in the thorax ; as is usual, the left face was flushed and the

Temperature and pulsation in left cervical sympathetic paralysis.

		Left side.		Right side.	
		Temperature.	Capillary pulsation.	Temperature.	Capillary pulsation.
Lip (angle) ...	...	36·5°	vivid	34·9°	vivid
Forehead ...	...	34·7°	distinct	33·5°	slight
Cheek ...	...	34·4°	v. distinct	32·8°	slight to distinct
Nose ...	...	34·0°	v. distinct	32·2°	slight
Side of chin	...	34·4°	distinct	33·4°	slight
Lobe of ear...	...	35·3°	v. distinct	35·2°	distinct
Temple ...	...	34·5°	v. distinct	33·4°	slight
Upper eyelid	...	34·2°	slight to distinct	32·8°	slight
Averages ...	...	34·7°		33·5°	

Rectal temperature 37·6°   Room temperature 17°
Blood pressure ... 174 (systolic) 110 (diastolic)

left pupil and palpebral fissure small by comparison with the right. Capillary pulsation was much more conspicuous on the left than on the right side of the face.

The obvious relation to warmth of the skin led me to investigate the influence of temperature upon it systematically (*160*). The hand is laid in water as hot as can be tolerated for three minutes ; it is removed, lightly dried and at once examined, using a glass slide. Capillary pulsation is seen almost always, but varies in its vividness, in these circumstances. It is missed only in subjects of middle and advanced years. If found only on close inspection, and then usually confined to the pads of the fingers, I call it " slight " in the accompanying table. If it is quite distinct in the finger tips and slight in a few other parts of the hand, such as the thenar and hypothenar eminences, it is marked " distinct." If it is distinct or vivid in the finger tips, and if it occurs over the whole or many parts of the skin of hands or fingers, it is marked " conspicuous."

The following table displays no relation between "capillary pulsation" and pulse pressure ; but there is an obvious though not wholly constant relation to age. In those ranging from 17 to 35 years, it is shown most fully and with much uniformity in its degree. As age advances into and beyond the forties it becomes less evident and many instances are encountered in which it is but slight or absent. A single exception to the rule that conspicuous pulsation fails to appear after 45 years was observed in an active man of 60 years.

R

Reaction of hand to hot water at 45 to 47° C. for 3 minutes.

No.	Age.	Capillary pulsation.	Blood pressure.		Pulse pressure.
			syst.	diast.	
1	17	conspicuous	135	95	40*
2	19	conspicuous	110	75	35*
3	23	conspicuous	126	86	40
4	24	conspicuous	130	85	45*
5	25	conspicuous	115	80	35
6	25	conspicuous	138	95	43
7	27	conspicuous	125	90	35*
8	29	conspicuous	130	100	30
9	30	conspicuous	118	90	28
10	31	conspicuous	135	85	50
11	32	conspicuous	115	85	30
12	34	conspicuous	104	70	34
13	35	conspicuous	138	90	48*
14	35	conspicuous	115	85	30
15	38	conspicuous	118	85	33*
16	38	slight	115	85	30
17	39	distinct	135	85	50
18	41	distinct	118	85	33
19	42	distinct	127	88	39
20	43	conspicuous	124	85	39
21	43	slight	158	115	43
22	46	distinct	132	87	45
23	46	slight	135	90	45
24	46	slight	124	95	29
25	46	absent	125	95	30
26	52	distinct	145	100	45
27	53	slight	125	85	40
28	56	slight	136	87	49
29	57	distinct	125	75	50
30	57	absent	125	90	35
31	57	distinct	145	95	50
32	60	distinct	145	90	55
33	60	distinct	140	90	50
34	60	conspicuous	138	95	43*
35	61	absent	140	100	40
36	61	absent	120	95	25
37	74	absent	105	55	50
38	76	absent	148	92	56
39	84	slight	124	95	29

* Pulsation in the fingers before heating.

Dilatation of small arterioles responsible.

Reviewing the evidence as a whole, the arterioles are clearly indicated as chiefly concerned in producing capillary pulsation ; the occurrence of the phenomenon in skin subjected to heat points to a purely local vascular change. This view is corroborated by further observations. Widening of the main vessels of the limb plays little or no part. Thus, if the whole arm is laid in a hot bath, with the hand projecting above the water level, capillary pulsation is not induced in the unimmersed part. If the whole arm or hand is immersed, with the exception of the last phalanx of one or more fingers, pulsation does not occur in the unimmersed finger tip ; nevertheless, the digital arteries are perceptibly widened in this test, pulsating more vigorously.

If the last phalanx of a finger, or no more than the pad of a finger, is alone held in hot water, pulsation appears in the submerged part. The area that it is necessary to heat is very small. Thus, when an unfiltered and powerful beam of light, sufficient just to sting, is allowed to fall on a few square millimetres of skin, the skin soon throbs perceptibly to the subject and capillary pulsation appears in and is confined to this small area.

Firm strokes of the skin often produce, as we have seen, a vivid red reaction, surrounded by a spreading flare ; the puncturing in of histamine has a similar result. After both forms of stimulation the skin temperature is raised and in the area of flare capillary pulsation is usually visible. The higher the temperature attained, the more conspicuous is pulsation.

It is found in small areas of inflamed skin ; thus, in young and healthy men, the pulsation may be found confined to the immediate neighbourhood of small cuts or scratches, such as are produced in shaving, and in the familiar acne pustule (*95, 160*) ; especially is it in evidence if these small lesions are surrounded by a small area of flush ; the temperature of these little pulsating areas is found to be from 0·5° to 1°C higher than that of the surrounding skin (*160*). These observations all go to show that the cause of capillary pulsation lies mainly in the skin itself, and while pointing to arterioles indicates those of small calibre.

Vessels of two orders are seemingly involved. It is necessary that the skin should be well coloured with blood for the phenomenon to be at all conspicuous ; the minute vessels must be open, in fact dilated. Simple dilatation of these vessels does not suffice however, for capillary pulsation is rarely to be seen in stroke reactions that fail to include not only a local red line but a surrounding flare as well. In elderly people, whose skin when heated fails to present capillary pulsation, reddening is nevertheless full. In reactive hyperæmia capillary pulsation is usually slight or absent.

When the skin temperatures associated with capillary pulsation are considered, it becomes necessary to assume the involvement of arterioles of larger size than the terminal arterioles (*see* Chapter XVI). When we consider the smallness of the area to which capillary pulsation may be confined, we may not assume the involvement of vessels larger than the branches of the arched arterioles. It is to the subpapillary plexus of arterioles or to these and the branches named that the phenomena may in all probability be attributed mainly.

The constant appearance of capillary pulsation in response to heat in the skin of young people and its inconstancy in the elderly, indicates that in the latter sufficient dilatation of the particular arterioles involved does not occur on heating, and further suggests that these vessels are incapable of expanding, relatively or absolutely. The idea has been put forward that the appearance or non-appearance of the reaction in the circumstances described, may serve to test the state of the vessels in question (*160*).

The vessels displaying pulsation.

The term capillary pulsation assumes that when skin presents a visible flow and ebb of colour with the pulse beats, the vessels displaying this pulsation are capillaries; it dates from a time when all vessels giving colour to the skin were thought of and classed as capillaries. Used in this sense the term is appropriate enough, since it is manifest that only vessels contributing to skin colour can aid in producing visible pulsation.

A point of chief present day interest is how far the pulsation can be traced from arterial to venous side. That the anatomical capillaries are involved is now almost universally recognised; it has been seen microscopically and described by a large number of workers (*27, 89, 124, 125, 243*), in the skin of the nail bed, of the arms, and of the cheeks, and in the mucous membrane of the lips.

The appearances vary according to the degree of colour change. If this is slight or at the moment invisible, the pulsation may be confined to the afferent limb of the capillary loop, the blood corpuscles being jerked sharply forward at each beat of the heart; if there is no blood flow through the loop, the corpuscles may move rhythmically to and fro in the afferent limb only, while those in the efferent limb remain at rest; this confined movement may usually be brought about by exerting greater pressure on the area examined. When the flow is freer and pulsation as a whole more manifest, the movement is also transmitted a greater or lesser distance along the efferent limb; the loop as a whole swells and its two limbs separate a little from each other at each beat (*243*). It is clear in such instances from close inspection that the pulsation is transmitted from arteriole to capillary in the direction of the blood flow; it is equally clear, when the movement of blood in a loop is temporarily reversed, as it may be under the condition of greater external pressure, that the pulsation is now opposed to the direction of blood flow. When skin pulsation is vivid, large numbers of capillary loops may spring into view in the microscopic field with each beat of the pulse, to vanish again in the pulse interval.

Now rhythmical increase and decrease of the blood content of the anatomical capillaries, will not always suffice to produce visible pulsation of the skin, for skin colour, as we have seen, is chiefly contributed by the minute venules. As Boas (*26*) pointed out, these vessels must therefore be involved. In favourable instances their participation can be seen.

An effective method is to apply a blister to the skin and, when the horny layer has risen, to remove it and cleanse the surface of the underlying epidermis. This method yields a clearer and deeper view of the vessels, but also dilates the vessels and causes pulsation to appear in them; thus it is ideal for the purpose. Liquid paraffin is laid on the bare surface; this is then covered with a sheet of plate glass gently pressed down and fixed at a point that yields distinct or conspicuous pulsation of the area. Examined microscopically, the pulsation can now be traced, according to its degree,

not only into the capillaries, but into the collecting venules, and into many parts of the subpapillary venous plexus (*160*). Exceptionally I have seen the plexus as a whole spring into clear view at each pulse beat. The distance through which the pulsation travels varies with the amount of external pressure ; the pulse travels farthest when pressure is light. How far it may travel when no external pressure is applied cannot be ascertained, for, when the rate of blood flow in the minute vessels is very rapid, the events can rarely be determined.

In outdoor workers the superficial venules of the cheeks are often of sufficient size to be seen easily with the naked eye ; if this facial skin is displaying colour pulsation, a little pressure on the venules will often disclose a rhythmic systolic widening of these vessels.

It will be remembered that Claude Bernard (*18*) saw the blood issue in bright jets from the veins of the submaxillary gland on stimulating the chorda tympani ; but this observation is not necessarily to be interpreted as a pulsation transmitted through the capillaries. At each pulse beat the swollen gland will become more tense and the pressure within, as it rises abruptly, may be sufficient to eject blood from the veins. Quincke's observation (*210*) upon the veins on the back of his own hand is perhaps clearer. He saw these veins pulsate from time to time, when his hand was much congested by heat, and ascertained that this pulse was centripetally in the veins.

It is beyond doubt that pulsation may be transmitted from the arterioles of the human skin, not only into the capillaries, but through these into the superficial venules ; further, it seems probable from the last observations quoted, observations that have been confirmed on many occasions, that in some circumstances it may be transmitted even to the relatively large veins that lie deeper than the layers of the true skin. Transmission to the venous side through the capillaries is not held to occur by all, however (*26*).

When it was suggested (*26*) that the venules are involved it was also suggested that the pulsation might be transmitted to them, not through the capillaries, but through certain arteriole-venule anastomoses first described by Sucquet (*242*) as occurring in the deeper layers of the skin. If the involvement of the venules in pulsation were so brought about, the pulsation of their contents would be retrograde, and should be confined at times to the efferent side of the capillary loops. Such movements I have never personally witnessed ; those that I have very frequently seen have been of a character strongly opposed to the view that the pulsation often reaches the capillaries from the venules.* The anastomoses in question are of macroscopic or almost macroscopic size and were originally stated to occur in many parts of the body, but Hoyer (*121*) and Grosser (*100*) working later, while finding

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* Retrograde pulsation has lately been described by Heimberger (*112a*) in individual capillaries and referred by him to shorter communications between the arterial and venous sides. The appearances he saw are sufficiently explained on the basis of communications of the capillary order (see page 2).

them in the pads of fingers and toes of man, have not extended their con-
firmation to other parts (*see also 231a*) ; yet pulsation of the venules has been
seen in the skin of the arm and in other places. I conclude therefore that
Sucquet's anastomoses play no part in producing the phenomenon.

To sum up this chapter, colour pulsation of the human skin occurring
in rhythm with the heart is a frequent phenomenon in normal subjects ;
rarely, it may be seen in untouched skin, much more frequently it is to be
elicited by gentle pressure. It is mainly caused by dilatation of small
arterioles in the skin, probably by the subpapillary plexus or by this and the
branches of the arched arterioles ; its presence may be used as evidence of
such dilatation both in health and in disease. If the skin of vascular parts
such as that of the palm of the hand is heated and fails to display
pulsation, a failure not infrequent in aged skin, it is probable that the
arterioles in question are incapable of dilating to their full natural extent.
The vessels displaying pulsation are all those that contribute to skin colour,
capillaries, collecting venules and subpapillary venous plexus ; the pulsation
is transmitted through these in the order stated and may proceed farther in
the direction of the subcutaneous veins.

CHAPTER XXI.

BIER'S SPOTS.

In 1898 Bier (23) described a curious phenomenon. He produced a slight venous congestion in the arm by winding a rubber bandage around its upper part ; then he tightened the bandage abruptly to occlude the brachial artery. The limb soon became cyanosed, but in about 15 minutes a number of white spots appeared in the skin. He explained these white areas as caused by contraction of the vessels in response to the stimulus of venous blood contained in them. In the same paper he described the phenomena of reactive hyperæmia, and explained the red flush that occurs when the circulation is released as a dilatation of the vessels in response to the stimulus of entering arterial blood. These spots have been investigated by Rehberg and Carrier (214), and by Miss Wolf (269), who worked in my laboratory ; I also have made many observations upon them.

If the tourniquet, or preferably a pneumatic armlet, is placed upon the upper arm and the artery obliterated as in Bier's original experiments, the spots that are found on the cyanosed skin below the obstruction are, as Rehberg and Carrier point out, of two kinds. Some are red and some are white.

The red spots.

These usually appear within a few minutes of the obstruction and are most frequently seen upon the wrist, fingers and palm of the hand, though others occur on the forearm itself. They are really of a dull red colour, but appear bright by contrast with the adjacent cyanosed skin (269) and recur with considerable regularity in the same places in repeated tests. They are due, as Rehberg and Carrier first suggested, to blood entering the forearm through the anastomotic circulation in the bones. Thus, Miss Wolf has shown that the skin of these spots is slightly warmer than the surrounding skin, and that they do not appear if the circulation to the limb is stopped by using a wide armlet that enwraps the elbow joint. The actual amount of blood escaping into the limb when the armlet is on the upper arm is in fact minute in quantity, amounting in a tested case to 0·025 cc. per minute to each 100 cc. of tissue (269). It is inconceivable that the blood that enters, being of such minute quantity, itself reaches the skin of the hand ; what happens is this. Blood flows into the humerus and flows out through small collateral arteriolar channels at the elbow to re-enter the main vessels of the arm and forearm ; in these it creates a slight forward flow. The bright

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Fig. 76. *Bier's white spots.* ($\times \frac{10}{21}$). A pressure of 30 mm. Hg having been thrown upon the veins of the forearm for a half minute, the circulation to forearm and hand was then stopped by forcing the armlet pressure far above systolic blood pressure. The photograph shows the condition of the arm 20 minutes later ; room temperature 19°C. The skin of the forearm and hand below the armlet was for the most part deep purple in colour, and presented innumerable white spots, irregular in size and form. The small dark spots were freckles.

Fig. 76.

blood, showing here and there in the skin, is the oxygenated blood that lies in this state in the arteries and arterioles of the limb during the experiment ; it is pushed forward by the leak into the vessels in the region of the elbow.

The white spots.

The white spots, and these are of main interest, develop later than the red, and are variable in their number, distribution and conspicuousness in different subjects and in different circumstances. No part of the limb is exempt from them. Some are usually to be seen at the end of a 5 minute compression, a few may appear as early as the end of the 2nd or 3rd minute. Their number increases as time goes on, the blanching becomes more vivid, and the spots grow in size and often coalesce to form large pale areas. In some individuals the hand shows them most strikingly, in others the forearm. They are irregular in form (Fig. 76, page 277). Their occurrence is not prevented by transferring the compression armlet from the upper arm to the elbow, thereby occluding anastomotic vessels.

Miss Wolf (*269*) conducted a number of very careful observations in which the outlines of spots were marked on the skin, for comparison with later tests ; she came to the conclusion that in repeated observations upon the same subject the spots do not reappear in the same places. With this conclusion I am not in entire agreement. It is true that in general and from day to day the same areas are not always, or even usually, involved, but if the tests are repeated at shorter intervals, recurrence of the original spots is far more frequent than can be accounted for by coincidence, and the shorter the interval the more exact is the correspondence. In more than one subject upon whom the tests have been repeated at half hourly or shorter intervals, and who presented very vivid and numerous areas of blanching, the pattern was repeated with remarkable accuracy of detail, and certain areas were involved over and over again from day to day. The distribution is by no means entirely haphazard. Blanching is particularly prone to occur over the main subcutaneous veins of the forearm, especially over the large radial vein, and here in the early stage of compression a group may appear to form a line of spots marking out the course of the vein. On the forearm it is not infrequent in counting to find at least half of them precisely over the courses of two or three of the main subcutaneous veins.

Meaning of Bier's spots. I am unable to reconcile the phenomena that these spots present with any hypothesis that has been put forward to explain them. Bier believed that the vessels are sensitive to the quality of blood they contain, and that they welcome arterial and reject venous blood. His explanation of his observations upon reactive hyperæmia, from which his more general hypothesis is derived, has been criticised destructively and in detail by Krogh (*137*) and by Rehberg and Carrier (*214*),* and there can be

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* The same workers have, I think, disposed of Zak's evidence (*271*), which was brought forward in support of Bier's view.

no doubt that his general hypothesis is incorrect. The change in the vessels in response to obstruction of the circulation through them has been considered fully in Chapter XII; we possess irrefutable evidence that the loss of vascular tone displayed by reactive hyperæmia occurs during the period of obstruction and not, as Bier supposed, at the moment of release.

Krogh, Rehberg and Carrier propound an alternative hypothesis; they believe that the white spots are due to a reaction of the vessels to cold, basing this view upon observations that the spots are more frequent if the skin is immersed in cold water at 5° to 7°C than if water at 44°C is used. The effects of temperature were more fully investigated by Miss Wolf, who found that the spots appear over the full range of temperature between 5° and 32°C, agreeing with Rehberg and Carrier that they become more numerous as the temperature is lower. She states that there is a critical temperature, lying in different instances between 33° and 36°C, above which white spots do not occur; Rehberg and Carrier saw them appear at 35°C. That there is a relation to temperature is beyond question but, as Miss Wolf has pointed out, temperature is not the only factor concerned. The argument is that if temperature alone were concerned, the whole of the skin would become blanched at the lower temperatures. "At a given moment the vessels in certain areas are ready to respond by contracting when a particular temperature is reached; other areas fail to respond similarly at this temperature and will not respond even though much lower temperatures are reached." To this argument, which I think to be essentially sound, I add the following arguments and observations.

The blanching that constitutes the conspicuous Bier's spot is a far more intense blanching than is seen in simple responses to cold; the latter is usually trivial. Bier's spots may appear, as has been stated, when the arm is immersed at 35° or 36°C; here the arm is not cooled, for its natural surface temperature lies below these points. I have occasionally seen Bier's spots appear upon skin to which the circulation has been stopped and which has been long immersed in water at 41° and 43°C, that is to say, in decidedly hot water. Finally, there are observations of which the following is an illustration. The circulation to an arm is obstructed and the arm allowed to remain at room temperature (18·5°C). The first Bier's spot is seen at 3 minutes, at 7 minutes there are 6 conspicuous and many less distinct spots on the forearm and a few faint ones on the hand. The hand is plunged into water at 43°C at the 8th minute; an almost immediate intensification of the faint spots on the hand begins and others soon appear. By the 10th minute the hand is vividly and universally mottled with brilliant white spots and areas of purple skin, the latter being distinctly darker in colour than any part of the skin at its immersion. In many other and similar immersion tests, in which the water used was of slightly lower temperatures (38° to 40°C) I have seen the Bier's spots remain or increase in distinctness, and some of these immersions have continued for at least 5 minutes. From time to time some of the spots are seen to fade after long immersions, but that is not

the rule. In these observations it is noteworthy that the vessels lying in areas outside those of the Bier's spots dilate in response to the warmth or heat ; those within the areas of the spots as a rule do not, they remain contracted or the contraction is increased.

The influence of temperature upon the development of Bier's spots is evidently complex ; a proper conception of the observations described is arrived at I think in the following way. The general and strong tendency of the vessels of the limb is to dilate during the period of circulatory arrest, in response to normal metabolites accumulating in the tissue spaces (see Chapter XII) ; but in the regions where Bier's spots develop the vessels react to an influence at present imperfectly understood, but one that acts in strong conflict with that of the vasodilator substances. The reason why cold predisposes to the Bier's spot is that it slows down the metabolic processes that are responsible for the vasodilator substances ; * it is not the cause of vasoconstriction.

It seems to me a matter of very considerable consequence that the real cause of these local vasoconstrictions should be found ; the preceding statement emphasises the importance of this unknown factor, for it is one which is capable of acting very powerfully and of acting effectively against opposing influences. I have been unable to prove the cause, but have been able to exclude certain theoretical influences, and to accumulate some evidence that may be of use to other workers.

The vessels of the skin affected by the Bier spot are evidently those responsible for skin colour. Microscopic examination of the skin (*214*) shows that the minute vessels decrease in size or disappear. This is due to an active change in them, to their contraction, as Bier rightly concluded, since blanching occurs while the circulation is at a standstill.

That contraction of the capillaries and minute venules is not the result of a central nervous influence, Bier has demonstrated ; that it is not the result of local nerve influence, observations that I made with Miss Wolf have shown. In examining for another purpose two cases of old standing nerve injury, one of the ulnar and one of the median nerve, areas of completely insensitive skin were mapped out on the hand. On occluding the circulation to these arms I noticed that Bier's spots appeared on the insensitive skin, and drew Miss Wolf's attention to the fact. As she has reported (*269*), the sensitive and insensitive skin were equally affected and single areas of blanching lay in part on normal skin and in part on skin to which the nerves had degenerated.

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* The reason why Bier's spots tend to appear especially over the course of the main veins of the forearm is, I think, that this skin has long been cooled by blood passing up these veins from the colder hand. I state this with some diffidence, for although the temperature of veins, over which the spots particularly tend to appear, is found beforehand to be less than that of the surrounding skin, yet I have been unable materially to influence the appearance of the spots over the veins of the forearm by previously immersing the hand either in cold or in hot water for periods of 10 minutes.

With cold and a local nervous reflex excluded as primary causes of Bier's white spots, we are left, by exclusion, with a chemical causation. This I adopt as the most probable explanation, and suggest that in skin deprived of its circulation vasoconstrictor substances, as well as vasodilator, are formed. I am not supposing that these substances are formed in different territories, but that both are formed in all; this it is necessary to assume.

Thus, when the circulation is released in an arm, on which the white spots are standing, it is the rule for the whole arm to flush vividly; the flush suffuses and obliterates the Bier's spots. These areas show no very definite tendency to fade first; usually, once the reactive hyperæmia has appeared, all trace of the spots is lost, then and subsequently.

Rehberg and Carrier have stated that they fade first. In repeated tests in five subjects I have failed to find this at all clearly. Usually it can be stated quite definitely not to be the case. If the Bier's spots are but faintly marked, very great care must be exercised to discriminate between them and previously pale areas of skin. Paler markings are quite common on the normal arm and when prominent help to constitute the mottling described in the Chapter XIII. If a little venous pressure is thrown on such an arm and the circulation is arrested, as in Bier's experiment, these paler markings are apt to appear more clearly and to be confused with Bier's spots. Moreover, if the circulation is released after a few minutes, the hyperæmia is frequently seen to fade away from these paler areas first. It is often necessary in counting Bier's spots on the arm, or in observing various influences upon them, to mark every pale area of the skin before starting the observation. It is further to be stated that the *red* spots appearing on the hand and arm often fail to react fully by flushing at the release, and nearly always lose the flush earliest; that is very natural, because they have received fresh blood during the period of brachial compression. The discrepancy between my statement and that by Rehberg and Carrier, probably finds its explanation in one or other or both of the directions indicated.

From this it is concluded that the skin of the Bier's spot has, at the time of circulatory release, a full content of vasodilator substances; and that these are universally and almost uniformly concentrated in the skin.

The reason why it must be assumed that vasoconstrictor substances are also present uniformly is as follows. The longer the skin is deprived of its circulation, the greater is the area invaded by the spots; although it is not feasible to show, on the living subject, that the whole skin will eventually become affected, yet it is clear that this will happen. It happens when the general circulation stops at death. If at the moment of death the skin is in a congested state, then, shortly after death Bier's spots appear. They

spread and coalesce until all but dependent parts of the skin * are involved, and the skin becomes universally blanched.†

There remains to be explained, in the experiment on the living subject, why, if vasoconstrictor substances are locally in excess in the Bier's spot areas at the time of release, these spots flush fully at the release. I think the reply to this can only be that the constrictor substances are very rapidly removed once blood enters the vessels. Bier's spots do not always flush in the reactive hyperæmia; the very palest, and especially those occurring on greatly cooled skin, are apt to prove resistent to the entry of blood. My view is that if any fresh blood enters the vascular territory of the Bier's spot, the predominant vasoconstrictor influence is lost almost at once, and that only those spots into which no fresh blood can enter resist joining in the reactive hyperæmia.

If a white spot proves resistant, it becomes possible to ascertain that its vessels will withstand high venous pressure; I have known them to persist despite lifts in this pressure to 70 or 80 mm. Hg. The contraction in them is a full contraction.

On the other hand, if Bier's spots are standing on the arm, the circulation to which is stopped, it will frequently be observed, if a white spot is pressed with the finger—and sometimes very light pressure will suffice—that on removing the finger the spot promptly disappears. The fact was first pointed out to me by my colleague Dr. Grant. The mechanical stimulus is in itself insufficient to cause a reaction of the vessels, but it may be presumed sufficient to displace a little blood from the vessels and to allow a little fresh blood to enter subsequently. This influx of fresh blood, so I presume, rids the territory of its excessive concentration of vasoconstrictor substances by diluting them.

The suggestion at once comes that the vasoconstrictor substances may be formed in the blood itself, rather than in the tissue spaces, in which case we should in reality return to Bier's view, that the vessels repel venous blood because it is venous. Certain considerations teach us that this is not so. It would be assumed that during circulatory arrest vasodilator substances are formed in the tissue spaces, that vasoconstrictor substances are formed in the stagnant blood, and that sooner or later the effective concentration of the latter exceeds that of the former. At the release of the circulation to the limb, new blood entering the vessels of the white spot would remove the constrictor substance entirely and leave the vasodilator substances free to act in their accustomed manner. But a similar explanation could not be

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* Or parts bruised during life, a phenomenon well known to forensics, and due, I imagine in part to the high content of H-substance in the affected skin.

† Thus it is probable that in any portion of skin deprived of its circulation for a sufficient space of time, contraction of the minute vessels will occur. The dead whiteness of the fingers in Raynaud's disease is almost certainly produced through a similar mechanism; simple closure of the arterioles will not suffice passively to blanch the skin to the degree seen; there must be in addition an active and strong spasm of the minute vessels themselves. Such a spasm is to be expected after the flow of blood to the skin has ceased for some while.

applied to the effects of light pressure on the Bier spot, for the blood entering would be small in quantity and also stagnant. It could of course be assumed that only such blood as stood in contact with the tissues, blood contained in endothelial vessels, developed these vasoconstrictor substances, a gratuitous assumption and a supposition which can in fact be disproved.

If Bier's spots are standing on the arm when the circulation is released and the circulation is reobstructed after the flush has become full and has obliterated them, these spots appear again and almost always in identical places ; moreover *they appear in as short a time interval as they did after the original arrest of the circulation.* Now we have been postulating that at the moment of release the tissue spaces are occupied by vasodilator substances at a certain concentration, and, since the reactive hyperæmia takes a long while to decline, we must allow that a minute or two after the release, this concentration of vasodilator substances in the tissue spaces is still considerable. Thus, at the second obstruction they will begin to accumulate from a point of concentration higher than at the beginning of the first, and should therefore be of greater concentration at each stage of the second than at the corresponding stage of the first test ; in both instances they will be balanced at first against blood containing no vasoconstrictor substances, beyond what may be present in fresh blood. In such circumstances it is clear that the appearance of Bier's spots in the second circulatory arrest should be longer delayed than in the first. That is not the case ; on the contrary, they appear if anything earlier.

My hypothesis therefore takes a different form. I imagine that both vasodilator and vasoconstrictor substances are released in the *tissue spaces* during circulatory arrest, and that the skin is universally affected ; that the vasodilator substances, which are regarded as normal metabolites, at first predominate, but that as time goes on their formation becomes retarded while the formation of vasoconstrictor bodies does not, or that these are late arrivals. Thus, at first the vasodilator substances are in excess, later a balance is struck and here and there the vasoconstrictor bodies begin to take effect and Bier's spots begin to appear. Eventually the whole skin will become white. The vasodilator substance is judged to be diffusible, but only slowly diffusible, as explained in Chapter XII. The vasoconstrictor substance I imagine to possess greater diffusibility. So, at the re-entry of blood, even in small quantity, a little lowering in the concentration of the more diffusible substance will occur and the balance will at once swing to vasodilatation. On reclosing the circulation, the tissues will still hold vasodilator substances predominantly ; thus the Bier's spots will reappear only when the balance is once more reversed by the gradual gain of vasoconstrictor concentration. The conception might be helped perhaps by considering the vasoconstrictor bodies as abnormal substances formed only when the tissues are deprived of nourishment for some while and are already in the initial process of death.

The explanation now put forward is of course of a hypothetical kind, but it is the simplest which I have been able to devise to cover the phenomena

that so far have been observed, and it is, I think, consistent with all these. Thus it would afford a reason why the activity of the skin before the circulation is stopped affects the result, as Miss Wolf showed ; previous flushing of the skin by warmth or friction tends to prevent Bier's spots from developing. This may well be due to their output of normal vasodilator bodies being greater and continuing to be greater than usual from the moment of compression.

Teleologically the hypothesis appeals because, while the mechanism would ensure local vasodilatation, the quicker diffusion of the vasoconstrictor substances into the general blood stream would tend to maintain an effective general pressure and a full blood supply to the part previously deprived of it.

Even if the explanation proves inadequate or untrue, it may perhaps serve as a starting point for further observations.

CHAPTER XXII.

REMARKS UPON SOME MORBID ERUPTIONS OF THE SKIN.

THE scope of this book is mainly physiological, but it is impossible long to contemplate the responses of the cutaneous vessels to simple stimuli, without being brought into contact with problems of especial interest to those who study the diseased skin, and without wishing that attempts should be made to test the applied value of these new notions. In the present chapter I shall endeavour to indicate a few directions in which the matter contained in previous chapters seems to me thus applicable. In pointing out the bearing that certain physiological observations may have upon the nature of skin eruptions, I may from time to time unwittingly express views already held, or views inconsistent with facts known to workers in this field of pathology. It is difficult to adopt the alternative course and to refrain altogether, while there exists the possibility that such remarks as it is proposed to make may prompt further study. I shall endeavour not to trespass unduly.

Types of reaction.

Because it is believed that the full vascular reaction of the skin to stimulation is triple, consisting of local vasodilatation, locally increased permeability of the vessel walls and the widespread flare, and that these three are separable, we might start in an attempt to synthesise the common skin eruptions, mixing these three ingredients in what we deemed suitable proportions. A very little reflection shows, however, that this plan would be unjustifiable since it would lack foundation in fact. It would carry us no nearer to our goal, which is to explain the diversity of skin eruptions as we see them. It would be the less justifiable because, although the three parts are separable in special circumstances, they are not separate as a rule. If we are to explain a number of apparently different eruptions upon a simple and common basis, then reasons must in each case be assigned why one part of the triple response is at times conspicuous, another dimly seen or perhaps absent.

A different plan will be followed and I shall divide the responses of the cutaneous vessels into two groups according to the order of vessel involved, and shall speak, therefore, in this connection of two chief types of reaction.

First type. This is a local reaction of the minute endothelial vessels covering precisely the area influenced by stimulation. It is independent of nervous intervention and in its complete form is twofold, consisting of active dilatation, and of increased permeability. The full colour shown in this is intense, but it is or rapidly becomes of a dull red or purplish hue. The reaction is due to a local liberation of our H-substance.

It is recognised, when it has already appeared, by its colour, by the crispness of its margins,* by the lack of striking evidence of increased blood flow, by its frequent association with a greater or lesser degree of swelling, by the reduced reaction of the vessels concerned to adrenalin and to histamine, and lastly by the colour spot reappearing speedily in its original form, when it is massaged away from skin to which the flow of blood has been stopped. This type of reaction tends especially to be followed by pigmentation.

Second type. This is the widespread flare resulting from the opening up of strong arterioles. It visibly consists of a diffuse scarlet blush of irregular outline, becoming speckled as it fades or while it lasts. It is due, *when provoked by local injury*, to a local reflex through the terminal branches of the sensory nerves, and then, like the first, is caused by H-substance released.

It is recognised, when it has already appeared, by its colour and diffuseness, by the size and distribution of its speckles, by the very distinct rise of skin temperature that accompanies it, by the fact that it is blanched when adrenalin or any other stimulus is used that brings the minute vessels to contraction and by the response of the affected skin to histamine being normal.†

Taken separately, these two types may be compared broadly to the two common forms of skin eruption, the macular or morbilliform on the one hand, the scarlatiniform on the other.

When the two types of reaction occur in manifest combination, as they frequently do in response to powerful artificial stimulation, for both are then provoked by the H-substance, they produce a composite eruption typified by the so-called urticarias.

It is concluded that all simple macular eruptions and all those of urticarial type are due, irrespective of their clinical associations, to the release of H-substance in the skin ; that the area covered by the crisp red spot, wheal or simple blister,‡ marks out with much precision the area of skin in which this substance has been released ; and that it is released in one of two ways, namely, either by direct injury of the cutaneous cells, as by external

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* Whenever the skin is uniformly reddened or blanched over a circumscribed area, which is bounded by sharply defined margins, it may be assumed that the minute vessels are actively engaged in producing the changed colour.

† The histamine must be held in place, however, until it has had time to act (see page 93).

‡ If the blister is surrounded by a crisply outlined reddening of the skin, then this area will usually mark out the area of release.

injury and as by circulating or entrapped poisons, or through the medium of antidromic impulses.

In considering the various forms of skin eruption that may be supposed to result from poisons (introduced through the circulation or directly from without), and in attempting to correlate these reactions with physiological types, there are several important matters for immediate or ultimate consideration. There is the distribution of such poison; there is its potency, a word here used in a special sense to signify the rapidity with which it injures living cells and liberates H-substance from these; there is the time that the poison lies in its active form in the skin; there is its diffusibility; there is the reactivity of the vessels and the nerve endings concerned to the H-substance released. These are the chief factors calculated to modify the reactions as we see them. These factors, and their supposed influences, will be considered briefly as they become relevant; and we may proceed forthwith and take up certain examples of cutaneous eruption and to discuss these upon the lines foreshadowed.

Certain cutaneous eruptions.

Urticaria. This consists of a more or less widespread erythema, in the centre of which a wheal develops. In its typical form, that here considered, it is an acute lesion. It would seem unnecessary laboriously to argue why I conclude that all lesions of this type, those that result from artificial stimulation and those that come as we say " spontaneously " are all due to a common cause, namely, the release of H-substance in the skin. The conclusion depends upon the presence of a common and triple end result. In the case of the spontaneous lesions, confirmation may be found in a defective reaction of the affected vessels to histamine and adrenalin in the stage of the lesion's subsidence.*

Here I am more concerned to explain on the basis of my theory the peculiarities of this rash. They depend upon its acuteness, and reactions to artificial stimuli, such as the stroke and freeze, suggest its being due invariably to the almost instant and full poisoning of the cutaneous cells, whereby H-substance is released quickly and in quantity. The acuteness of the reaction, with its rapid and high concentration of H-substance, explains the full development and visibility of the surrounding flare; the arteriolar dilatation helps to explain the quick outpouring of fluid to form a sharply defined and tense wheal. The rapid discharge of the dose of H-substance and the abrupt onset of refractoriness will sufficiently account for the relatively rapid subsidence of the rash.

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* I have actually tested two cases and there obtained these confirmations. In these cases, curiously, the tendency of the skin to wheal to the stroke stimulus was enhanced over the areas of spontaneous wheals, *while these were developing*. These observations should be pursued.

The macule. The macule I regard as representing a reaction of the first type, defining with precision the zone of release. In the raised macule œdema is added. Both these forms are slower in onset than is urticaria, both are more persistent. They are analogous to the ultraviolet burn, and are supposedly due to the presence of a stimulus (or poison) that acts with less potency and longer than is the case with urticaria, or to a stimulus that damages the cells slightly, but in such a way that they continue to liberate their H-substance content slowly and for relatively long time periods. In both these instances the low concentration of the substance in the tissue spaces will result in the appearance of a reaction of the minute vessel, while the surrounding flare fails, or tends to be concealed by a balancing action of the minute vessels themselves (see page 127).

The conclusion that this form of eruption also depends upon the release of H-substance rests primarily upon its precise resemblance to the ultraviolet burn, upon the fact that the reaction to this physical agency and that now discussed are readily explained as simple modifications of the triple response, and upon my own unpublished observations that the rash of measles shows refractoriness to histamine itself and irresponsiveness to adrenalin.

The absence of œdema or of conspicuous œdema is associated with the slow development of the skin's reaction, for in such instances arteriolar dilatation is not excessive.

The blister. This term is here used for the purpose of avoiding particular reference to the various herpetiform, pemphigoid, and bullous eruptions that are described ; it is not clear to me that lesions of these classes can be regarded as distinct from the standpoint of the ultimate mechanism that is involved in causing them ; it would seem safer to assume that they are produced by one essential cause. The blister replaces the wheal in a large number of instances in which the skin responds to simple forms of artificial stimulation ; reactions that are known to result, at all events in chief part, from the release of H-substance. Since increased permeability of the vessel wall forms one of the three fundamental parts of the vascular mechanism of defence in the skin, and since the blister, like the wheal, is a manifest sign of increased permeability, it seems reasonable on this ground alone to regard the blister as a simple variation in the form of response. The response to artificial stimuli indicates that blistering is especially associated with prolonged response, and it is suggested that this prolongation in itself determines blistering (see page 137). The precise determining factor of the blister, however, is still unknown.

Eruptions displaying blisters are usually, perhaps always, accompanied by a local vasodilatation, though the blister does not always cover completely the area of affected skin. The relation between these two parts of the triple response in spontaneous eruptions is a matter that would repay further study. The frequency with which spontaneous blisters are accompanied by signs, faint or otherwise, of a surrounding arteriolar flare is unknown to me ; this also should be ascertained.

Telangiectases. The meaning of telangiectases has been remarked upon earlier. The familiar port wine nævus is probably of allied origin. I regard these, for reasons set forth on page 256, and given fully in an article that deals with them in detail (*162*), as being extreme instances of a prolonged reaction, though fundamentally of the same type as the remaining local vascular responses to injury.

Hæmorrhagic eruptions. For reasons expressed by Miss Harmer and myself in an article (*168*) dealing at greater length with this subject than is here possible, I believe that hæmorrhage into the skin in large part results from weakness of the vessel walls ; that the latter is induced by damage of a kind akin to that which dilates these vessels or renders them especially permeable; and that any cause tending to produce the macule, the raised macule or the blister will likewise tend towards rupture of any of the minute vessels so affected and subsequently placed under strain. This same tendency is present in skin lesions produced by freezing, ultraviolet light and other forms of stimulation ; but its onset seems at times to be delayed beyond that of the full vascular dilatation and to be present in variable degree. According to this view a purpuric spot may sometimes conceal a macule, or may so change its aspect that it becomes unrecognisable as such. According to the same view, bleeding into the lesions of an exanthematous rash, or into other skin eruptions that are unassociated with the specific fevers, though it may signify severity of poisoning, does not imply a fundamental difference in the mechanism that underlies the lesions as a whole.

Scarlatiniform rash. As the type, I take the rash of scarlet fever itself. This rash consists essentially of a diffuse scarlet flare, tending to break up into minute speckles or islets, which, as I can assert, are of similar size and distribution to the corresponding speckles of the lasting flare of histamine. This flare of scarlet fever is abolished by adrenalin or by the minute vessel contraction that is obtained by gentle stroking (white reaction of Chapter II).

In eruptions of this kind it is suggested that the responsible poison acts, at all events in part,* either directly upon the sensory nerve terminations, as does histamine in the axon reflex, or upon the strong arterioles themselves. It seems necessary to make one or other of these assumptions because, if histamine or the H-substance is introduced into the normal skin by any means, and is present in sufficient quantity to stimulate the nerve endings and to produce a long lasting flare, it will also yield a local reaction of corresponding conspicuousness in the form of reddening and swelling ; whereas the last two elements of the triple response are inconspicuous in, or absent from, the rash of scarlet fever.

The scarlatiniform rash, in so far as it is unassociated with macules, must pass, therefore, to a category distinct from the eruptions previously considered.

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* I say in part because the so-called scarlatiniform rash is often combined with small macules and the origin of these would be explained on the lines previously laid down.

The form, and the change in form, of individual lesions.

The original form of a lesion will naturally depend, according to the views previously expressed, upon the size and shape of the area of skin in which H-substance is released in sufficient concentration to act.

The original form may be held or it may change. Slight changes may result by diffusion of the H-substance itself, as we saw in the instance of the ultraviolet light reaction ; but such movements are relatively small and are characterised by a rapid decrease in the intensity of the reaction as it is traced away from the original lesion. In this connection, however, it is to be remarked that lymphatic extensions may occasionally become dimly visible through this means. The œdema of urticarial lesions is a tense œdema, owing to the very rapid output of fluid ; this fluid may subsequently force its way a few millimetres distance at the most into surrounding unaffected skin, and thus pressure is relieved.

There are cutaneous lesions, however, that grow more extensively after erupting, and here the mechanism of movement is distinct. If an inflammatory lesion appears in the skin and creeps slowly through the skin, radially or in one direction, while the intensity of the reaction manifested is fully maintained at its moving edge, then the lesion is due to a poison that has been introduced into the skin, locally and not diffusely ; the poison is trapped in the skin and the marginal spread represents its restricted movement in the plane of the skin. For marginal advance indicates that the stimulus, to which the skin surrounding the original lesion is now responding, is reaching it radially from the original central focus; and no movement of H-substance, released at a centre point, will account for a form of progression in which the reaction is maintained at its full intensity. Further, if such poison has not been introduced directly from without, but has been brought to the skin through vascular channels, the poison is probably a bacterial agent and living. The most obvious example of such a spreading lesion is erysipelas, but other instances of creeping lesions should, I think, undoubtedly be interpreted upon similar lines.

A creeping lesion that is œdematous is apt to display a curious phenomenon ; as it grows it at first becomes depressed centrally, or umbilicated, and later takes the form of a wide circular rim of œdema. There is marginal spread, while the reaction subsides centrally. When two such lesions encounter each other in moving, they fuse ; the advancing ramparts do not pass through each other, as do meeting waves, but both here subside, and the combined lesions assume the form of a raised figure of eight. Further fusions, associated here and there with cessation of marginal spread and subsidence of the rampart, are similarly responsible for the curious gyrate figures or serpentine markings, so familiar to dermatology.

The umbilication and subsequent growth of the flat centre is not due to the original poison being exhausted centrally ; if that view were adopted, it would become necessary also to assume that the poison, still clearly

existing in the marginal skin, is free to move outwards but is debarred from moving inwards. It is due to the vessels that have first reacted gradually becoming refractory to stimulation and simultaneously losing their increased permeability.

Umbilication and more extensive central flattening is brought about in much the same way as are the minute craters described on page 99. The subsidence of the œdema in two ramparts that meet is similarly explained, the responsiveness of the tissue, and not the poison, is here exhausted.

Sometimes, seemingly, this unexhausted poison, of two colliding ramparts, travels further through skin that has already experienced it ; it then proceeds on its course but gives no sign of its presence until it meets fresh skin and thus, in the stage of subsidence of the lesions as a whole, a new crop of transient œdematous nodules may appear in the surrounding skin. An instance of this kind has been described fully by Zotterman and myself (*174*), and the truth of the above hypothesis demonstrated by the observation that in the central or depressed parts of the circular lesions, the vessels were actually refractory to the action of histamine.

The distribution of skin eruptions.

This subject will be dealt with briefly and from one standpoint only. In previous chapters I have dealt fully with the mottling of the skin as this is seen on the limbs and trunk. It is becoming increasingly manifest that these areas of mottling exert a very decided influence upon the distribution of skin eruptions. This matter has been dealt with by Adamson (*2*), to whose account we are chiefly indebted for our knowledge. The darker areas of the mottled skin are relatively unresistant. When exposed to prolonged heat the vessels undergo exaggerated expansion and the skin here pigments deeply (see Fig. 75, page 263 and corresponding text). The same dark areas are particularly apt to become indurated or to become the seat of actual tuberculous infection (*151*, *152*, *162*). Adamson and other workers have shown that the macules of certain syphilitic rashes are related in their distribution to these cutaneous markings, the former believing that the spirochætes settle down first in the areas of darker coloured skin. He has also suggested that the rash of measles follows similar lines ; personal observations convince me that in the early stages of this eruption the macules tend especially to appear in the dark reticulations of the skin, and I think the same is true of general urticaria (*168*).

It has long been known that there are areas of the face especially prone to certain skin eruptions. The malar triangles (see page 256) form areas that often sharply enclose the eruptions known as *lupus erythematosus* and *acne rosacea*. This distribution of facial rashes is usually and rightly related to areas that flush readily ; but this correlation does not fully display the significance of these areas. They are areas in which the vessels are *atonic* in the sense previously defined and this atony is associated with

other changes as previously shown. Miss Harmer and I have recently described (*168*) a remarkable instance of cutaneous hæmorrhage in a boy ; the purpuric eruption invaded the face and picked out symmetrically and with great precision the areas in question. As stated on page 290, this tendency to rupture is a common association of the atonic condition.

Here, it is desired particularly to emphasize that the vessels of the redder areas of the mottled skin of limbs and trunk are in similar condition to those of the atonic areas of the face (see Chapter XIX). When it is known why the inflammatory diseases named affect especially certain areas of facial skin, we shall be near to explaining, or shall have explained, why other eruptions or hæmorrhages tend to appear especially on the red reticulations of the trunk and limbs, why smallpox erupts especially on the two areas of skin that are chiefly exposed to sunlight (Finsen *83*), namely, the face and hands, and why, as has been demonstrated, previous injuries (for example the application of heat or of irritant substances) will determine the appearance of an eruption earliest or in confluent form in the skin so treated (Pirquet *205*). All these phenomena are closely linked together, and their common cause is to be found either in the peculiar predisposition of the vessels concerned to dilate farther, or in the manner in which the blood flows through them, or in a changed resistance of the cellular tissues that these vessels supply.

Which of these we shall assign as the cause, remains, with other problems relating to the cutaneous circulation, for the future to decide.

Centigrade and Fahrenheit equivalents.

Cent.	Fahr.	Cent.	Fahr.	Cent.	Fahr.
—30	—22·0	0	32·0	26	78·8
—25	—13·0	1	33·8	27	80·6
—24	—11·2	2	35·6	28	82·4
—23	— 9·4	3	37·4	29	84·2
—22	— 7·6	4	39·2	30	86·0
—21	— 5·8	5	41·0	31	87·8
—20	— 4·0	6	43·8	32	89·6
—19	— 2·2	7	44·6	33	91·4
—18	— 0·4	8	46·4	34	93·2
—17	1·4	9	48·2	35	95·0
—16	3·2	10	50·0	36	96·8
—15	5·0	11	51·8	37	98·6
—14	6·8	12	53·6	38	100·4
—13	8·6	13	55·4	39	102·2
—12	10·4	14	57·2	40	104·0
—11	12·2	15	59·0	41	105·8
—10	14·0	16	60·8	42	107·6
— 9	15·8	17	62·6	43	109·4
— 8	17·6	18	64·4	44	111·2
— 7	19·4	19	66·2	45	113·0
— 6	21·2	20	68·0	46	114·8
— 5	23·0	21	69·8	47	116·6
— 4	24·8	22	71·6	48	118·4
— 3	26·6	23	73·4	49	120·2
— 2	28·4	24	75·2	50	122·0
— 1	30·2	25	77·0	55	131·0

BIBLIOGRAPHY AND INDEX
OF AUTHORS.

PAGE

1. **ABEL** (J. J.) and **KUBOTA** (S.). "On the presence of histamine (B-iminazolylethylamine) in the hypophysis cerebri and other tissues of the body and its occurrence among the hydrolytic decomposition products of proteins."
Journ. of Pharmacol. and exper. Therap., 1919, XIII, 243-300. — 234.

2. **ADAMSON** (H. G.). "Modern views upon the significance of skin eruptions."
Lancet, 1912, I, 1041-1048. — 260, 261, 292.

3. **ALDRIDGE** (C.). "The ophthalmoscope in mental and cerebral diseases,"
West Riding lunatic Asylum med. Rep., 1871, 95-98. — 258.

4. **ANREP** (G.). "On the part played by the suprarenals in the normal vascular reactions of the body."
Journ. of Physiol., 1912-13, XLV, 307-327. — 171, 179, 181, 206.

5. **BARCROFT** (J.) and **KATO** (T.). "Effects of functional activity in striated muscle and the submaxillary gland."
Phil. Trans. Roy. Soc., 1916, B, CCVII, 149-182. — 187, 207.

6. **BARCROFT** (J.) and **PIPER** (H.). "The gaseous metabolism of the submaxillary gland with reference especially to the effect of adrenalin and the time relation of the stimulus to the oxidative process."
Journ. of Physiol., 1912, XLIV, 359-373. — 187, 207.

7. **BARDEEN** (C. R.). "A study of the visceral changes in extensive superficial burns."
Journ. exper. Med., 1897, II, 501-514. — 111.

8. **BARDEEN**. "On certain visceral pathological alterations, the result of superficial burns."
Johns Hopkins Hosp. Bull., 1897, VIII, 81-82. — 111.

9. **BARDY** (H.). "Über Hemmung inflammatorischer Symptome."
Skand. Archiv f. Physiol., 1915, XXXII, 198-216. — 68, 216.

10. **BARGER** (G.) and **DALE** (H. H.). "B-iminazolylethylamine a depressor constituent of intestinal mucosa."
Journ. of Physiol., 1910-11, XLI, 499-503. — 59, 105, 234.

11. **BARTHELEMY** (T.). "Étude sur le Dermatographisme ou Dermoneurose toxivasomotrice," Paris, 1893. — 46.

12. **BAYLISS** (W. M.). "On the origin from the spinal cord of the vaso-dilator fibres of the hind-limb and on the nature of these fibres."
Journ. of Physiol., 1900-1901, XXVI, 173-209. — 210, 211, 236.

13. Bayliss (W. M.). "On the local reactions of the arterial wall to changes of internal pressure."
Journ. of Physiol., 1902, XXVIII, 220-231. — 171.

14. **BAYLISS** (W. M.). "Intravenous Injection in Wound Shock," London, 1918. — 110.

15. **BAYLISS** (W. M.). "The vaso-motor System." London, 1923. — 207, 211.

16. **BAYLISS** (W. M.). "Principles of general Physiology." London, 1924, Ed. 4, p. 703. — 183.

17. **BEAUNIS** (H.). "Le Somnambulisme provoqué." Paris, 1886, p. 76. — 214.

PAGE

18.   BERNARD (C.). "Sur les variations de couleur dans le sang veineux des   273.
organs glandulaires," etc..
Journ. d. l. Physiol. d. l'homme e. d. animaux, 1858, I, 233-241.

19.   BERNHEIM. "De la Suggestion et de ses Applications à la Thérapeutique."   214.
Paris, 1888, p. 105.

20.   BEST, DALE, DUDLEY and THORPE. (In the press.) Journ. of Physiol..   59, 105, 234.
Dr. Dale has kindly given me in conversation a resumé of these
observations.

21.   BIEDL (A.) and KRAUS (R.). "Experimentelle Studien über Anaphy-   112.
laxie."
Wiener klin. Wochenschr., 1909, XXII, 363-370.

22.   BIER (A.). "Die Enstehung des Collateralkreislaufs." Theil I. Die   151, 172.
arterielle Collateralkreislauf."
Archiv f., patholog. Anat. u. Physiol., 1897, CXLVII, 256-293 and
444-474.

23.   BIER (A.). "Die Enstehung des Collateralkreislaufs." Theil II. Der   151, 172, 173,
Rückfluss des Blutes aus ischämischen Körpertheilen."   275.
Archiv f. patholog. Anat. u. Physiol., 1898, CLIII, 306-334.

24.   BLACHEZ. Bull. e. Mém. d. l. Soc. méd. d. Hop. d. Paris, 1873, IX,   56.
2nd ser., 270-271.

25.   BLOOM (W.) "Histamine as an inflammatory agent." Johns Hopkins   106.
Hosp. Bull., 1922, XXXIII, 185-188.

26.   BOAS (E. P.). "The nature of the so-called 'capillary pulse'."   272, 273.
Archives of internal Med., 1922, XXIX, 763-67.

27.   BOAS (E. P.). "Clinical capillary pulsation."   272.
Heart, 1923, XI, 57-60.

28.   BRESLAUER (F.). "Die Pathogenese der trophischen Gewebsschäden   32, 68, 69, 144,
nach der Nervenverletzung."   209.
Deutsch. Zeitschr. f. Chirurg., 1919, CL, 50-81.

29.   BROOKS (B.). "Pathologic changes in muscle as a result of disturbances   157.
of circulation."
Archives of Surgery, 1922, V, 188-216.

30.   BROOKS (B.) and JOSTES (F. A.). "A clinical study of diseases of the   230.
circulation of the extremities," etc..
Archives of Surgery, 1924, IX, 485-503.

31.   BROWN (W. E. L.) and HILL (A. V.). "The oxygen-dissociation curve   144.
of blood, and its thermodynamical basis."
Proc. Roy. Soc., 1923, B., XCIV, 297-334.

32.   BRUCE (A. N.). "Uber die Beziehung der sensiblen Nervenendigungen   67, 216.
zum Entzündungsvorgang."
Archiv f. exper. Pathol. u. Pharmakol., 1910, LXIII, 424-433.

33.   BRUENING (F.) and STAHL (O.). "Uber die physiologische wirkung   210.
der Exstirpation des periarteriellen sympathischen Nervenge-
flechtes (periarterielle Sympathektomie)."
Klin. Wochenschr., 1922, I, 1298-1300.

34.   BRÜNING (F.). "Über die Gefässnervenbahnen an der Extremitäten."   210.
Klin. Wochenschr., 1924, III, 2087-2090.

35.   BRUNS (O.) and KÖNIG (F.). "Uber die Strömung in den Blutkapillaren   141, 143, 147.
der menschlichen Haut bei kalten und warmen Bädern und über die
'Reaktion' in und nach kühlen Wasser-und Kohlensäurebädern."
Zeitschr. f. physik. u. diät. Therap., 1920, XXIV, 1-11.

36.   BURGESS (T. H.). "The Physiology or Mechanism of Blushing," London,   209, 258.
1839.

37.   BURN (J. H.) and DALE (H. H.). "The vaso-dilator action of histamine,   109, 231.
and its physiological significance."
Journ. of Physiol., 1926, LXI, 185-214.

38.   CALLANDER (C. L.). "Arterial decortication."   210.
Annals of Surgery, 1923, LXXVII, 15-29.

39.   CAMPBELL (H.). "Flushing and morbid Blushing." London, 1890.   259.

PAGE

40. CANNON (W. B.). "A consideration of the nature of wound shock." 110.
    Medical research Committee Rep., London, 1919, No. 25, 109-124.
    (The report contains many other valuable contributions to the same
    problem).

41. CANNON (W. B.). "Traumatic Shock," New York and London, 1923. 110.

42. CANNON (W. B.) and BAYLISS (W. M.). "Note on muscle injury in 110.
    relation to shock."
    Medical research Committee Rep., London, 1919, No. 26, 19-23.

43. CARRIER (E. B.). "Studies on the physiology of capillaries. v. The 17, 29, 31, 32,
    reaction of the human skin capillaries to drugs and other stimuli." 36, 37, 69, 142,
    Amer. Journ. of Physiol., 1922, LXI, 528-547. 143, 147, 188,
    198, 229.

44. CHAMBARD (E.). "Dermoneurose stéréographique et erythrasma chez
    un imbécile alcoolique."
    Archiv. d. Neurol., 1889, XVII, 8-21.

45. CHARCOT. "Érythème produit par l'action de la lumière électrique," 117.
    Compt. rend. hebdo. d. l. Soc. d. Biol., 1858, XV, Ser. II, 63-5.

46. CHARCOT. "Note sur quelques cas d'affection de la peau dependant 214.
    d'une influence du system nerveux."
    Journ. d. Physiol., 1859, II, 108 (Case 3).

47. CHATELAIN (E.). "Précis iconographique des Maladies de la Peau," 46.
    Paris, 1893, p. 400.

48. CLARK (E. R.) and CLARK (E. C.). "A. The development of adventitial 35.
    (Rouget) cells on the blood capillaries of amphibian larvæ,"
    Amer. Journ. of Anat., 1925, XXXV, 239-264.

49. CLARK (E. R.) and CLARK (E. C.). "B. The relation of Rouget' cells to 35.
    capillary contraction.
    Amer. Journ. of Anat., 1925, XXXV, 265-282.

50. COHNHEIM (J.). "Untersuchungen ueber die embolischen Processe." 151, 153, 185.
    Berlin, 1872.

51. COTTON (T. F.), SLADE (J. G.) and LEWIS (T.). "Observations upon 23, 24, 25, 29,
    dermatographism with special reference to the contractile power 31, 36, 37, 42,
    of capillaries." 47.
    Heart, 1915-17, VI, 227-247.

52. CRAWFORD (J. H.). "Studies on human capillaries. II. Observations on 197.
    the capillary circulation in normal subjects."
    Journ. of clin. Investigation, 1926, II, 351-364.

53. DALE (H. H.). "On some physiological actions of ergot." 207.
    Journ. of Physiol., 1906, XXXIV, 163-206.

54. DALE (H. H.). "The anaphylactic reaction of plain muscle in the 113.
    guinea pig."
    Journ. of Pharmacol. and Therap., 1912-13, IV, 167-223.

55. DALE (H. H.). "The activity of the capillary blood vessels and its 108, 110.
    relation to certain forms of toxæmia."
    Brit. med. Journ., 1923, I, 959-962 and 1006-1010.

56. DALE (H. H.) and LAIDLAW (P. P.). "The physiological action of 104, 108, 112.
    B-iminazolylethylamine."
    Journ. of Physiol., 1910-11, XLI, 318-344.

57. DALE (H. H.) and LAIDLAW (P. P.). "Further observations on the 108.
    action of B-iminazolylethylamine."
    Journ. of Physiol., 1911-12, XLIII, 182-195.

58. DALE (H. H.) and LAIDLAW (P. P.). "Histamine shock." 108, 112, 114.
    Journ. of Physiol., 1918-19, LII, 355-390.

59. DALE (H. H.) and RICHARDS (A. N.). "The vasodilator action of 18, 35, 108, 208,
    histamine and of some other substances." 209.
    Journ. of Physiol., 1918-19, LII, 110-165.

60. DARWIN (CHARLES). "The Expression of the Emotions in Man and 258.
    Animals." London, 1872, p. 310.

PAGE

61. DAVIES (H. M.). "The functions of the trigeminal nerve."   208.
Brain, 1907, CXVIII, 219-276.

62. DELBET (P.). Compt. rend. hebdo. d. l. Soc. d. Biol., 1918, LXXXI, 858-63.   110.

63. DENNIG (H.). "Enthalten die periarteriellen Nerven lange sensibile   210.
Bahnen ? "
Klin. Wochenschr., 1925, IV, 66-68.

64. DICK (G. F.) and DICK (G. H.). "A skin test for susceptibility to scarlet   133.
fever."
Journ. Amer. med. Assoc., 1924, LXXXII, 265-6.

65. DIXON (W. E.). "Discussion on the therapeutic value of light."   118, 135.
Brit. med. Journ., 1925, II, 499-500.

66. DOI (Y.). "On the existence of antidromic fibres in the frog and their   222, 224.
influence on the capillaries."
Journ. of Physiol., 1920-21, LIV, 227-238.

67. DONEGAN (J. F.). "The physiology of the veins."   142.
Journ. of Physiol., 1921, LV, 226-245.

68. DREYER (G.) and JANSEN (H.). "Ueber den Einfluss des Lichtes auf   118.
tierischen Geweben."
Mitt. a. Finsen's Lichtinstituts, 1905, IX, 180 (citation).

68a. DRURY (A. N.) and JONES (N. W.). "Observations upon the rate at which   111.
œdema forms when the veins of the human limb are congested."
Heart, 1927, XIV, 55-70.

69. DUBLER (A.). "Ueber Neuritis bei Herpes zoster."   213.
Archiv f. patholog. Anat. u. Physiol., 1884, XCVI, 195-234 (Case 2).

70. DUDGEON (L.). "Volkmann's contracture."   157, 185.
Lancet, 1902, I, 78-85 (Case 13).

71. DUKE (W. W.). "Urticaria caused by light."   129, 242.
Journ. Amer. med. Assoc., 1923, LXXX, 1835-1838.

72. DUKE (W. W.). "Urticaria caused specifically by the action of physical   56, 129, 241, 242.
agents."
Journ. Amer. med. Assoc., 1924, LXXXIII, 3-9.

73. DUKE (W. W.). "Allergy Asthma, Hay Fever, Urticaria and allied   116.
Manifestations of Reaction." St. Louis, 1925.

74. DUMONTPALLIER. "De l'action vaso-motrice de la suggestion chez les   215.
hystériques hypnotisable."
Compt. rend. hebdo. d. l. Soc. d. Biol., 1885, II, Ser. VIII, 434, 458, 597.

75. EBBECKE (U.). "Die lokale vasomotorische Reaktion (L.V.R.) der Haut   18, 31, 41, 44,
und der innere Organe."   51, 67, 69, 72,
Archiv f. d. ges. Physiol., 1917, CLXIX, 1-81.   74, 108, 188,
   189, 221, 260.

76. EBBECKE (U.) "Die lokale galvanische Reaktion der Haut."   83.
Archiv. f. d. ges. Physiol., 1921, CLXXXIX, 230-269.

77. EBBECKE (U.). "Über elektrische Hautreizung."   83.
Archiv f. d. ges. Physiol., 1922, CXCV, 300-323.

78. EBBECKE. "Capillarerweiterung, Urticaria und Schock."   80.
Klin. Wochenschr., 1923, II, 1725-7.

79. EBBECKE (U.). "Über Gewebsreizung und Gefässreaktion."   58, 70, 72, 83.
Archiv f. d. ges. Physiol., 1923, CXCIX, 197-216.

80. ELLIOTT (T. R.). "A case of traumatic herpes zoster."   213.
Brit. Journ. of Surg., 1915, III, 261-263.

81. EPPINGER (H.). "Über eine eigentumliche Hautreaktion, hervorgerufen   59.
durch Ergamin."
Wien. med. Wochenschr., 1913, LXIII, 1414.

82. FELDBERG (W.). "The peripheral innervation of the vessels of the   210, 224.
external ear of the rabbit."
Journ. of Physiol., 1926, LXI, 518-529.

83. FINSEN (N. R.). "Ueber die Bedeutung der chemischen Strahlen des   117, 118, 119,
Lichtes für Medizin und Biologie," Leipzig, 1899.   293.

PAGE

84. FINSEN (N. R.). " Neue Untersuchungen über die Einwirkung des   117, 256.
        Lichtes auf die Haut."
     Mitt. a. Finsen's Lichtinstitut, 1900. (Citation).

85. FLOREY (H.). " Microscopical observations on the circulation of the   31, 41, 108, 142,
        blood in the cerebral cortex."   221.
     Brain, 1925, XLVIII, 43-64.

86. FLOREY (H.). " Observations on the resolution of stasis in the finer   74.
        blood vessels."
     Proc. Roy. Soc., 1926, B., Vol. C, 269-273.

87. FLOREY (H. W.) and CARLETON (H. M.). " Rouget cells and their   35.
        function."
     Proc. Roy. Soc., 1926, B. Vol. C, 23-31.

88. FRASER (T. R.). " Urticaria a frigore."   56.
     Trans. Med.-Chir. Soc. Edinb., 1905-6, XXV, 90-92.

89. FREEDLANDER (S. O.) and LENHART (C. H.). " Clinical observations on   272.
        the capillary pulsation."
     Archives of internal Med., 1922, XXIX, 12-32.

90. FRIEDRICH (H.). " Was geht in einer Extremität nach der periar-   210.
        teriellen Sympathektomie vor sich ? "
     Klin. Wochenschr., 1924, III, 2035-40.

91. GASKELL (W. H.). " On the tonicity of the heart and blood vessels."   179, 187.
     Journ. of Physiol., 1880-2, III, 48-75.

92. GASKELL (W. H.). " The involuntary nervous System," London, 2nd   211.
        Ed., 1920.

93. GILCHRIST (T. C.). " Some experimental observations on the histo-   57.
        pathology of urticaria factitia."
     Journ. of cutaneous Diseases, 1908, XXVI, 122-123.

94. GLÄSER (W.). " Die Nerven in den Blutgefässen des Menschen."   221.
     Archiv f. Anat. u. Physiol., 1914 (Anat. Abth.), 189-196.

95. GLAESSNER (K.). " Klinische Untersuchungen über den Kapillarpuls."   267, 268, 271.
     Deutsch. Archiv f. klin. Med., 1909, XCVII, 83-103.

96. GOLDBLATT (H.). " Observations upon reactive hyperæmia."   157, 171, 181.
     Heart, 1925-26, XII, 281-294.

97. GOLDSCHMIDT (S.) and LIGHT (A. B.). " The effect of local temperature   142 to 146.
        upon the peripheral circulation and metabolism of tissues as revealed
        by the gaseous content of venous blood."
     Amer. Journ. of Physiol., 1925, LXXIII, 146-172.

98. GOLTZ (F.). " Ueber gefässerweiternde Nerven."   203.
     Archiv f. d. ges. Physiol., 1874, IX, 174-197.

99. GOLUBEW (A.). " Beiträge zur Kenntniss des Baues und der Entwick-   34.
        lungsgeschichte der Capillargefässe des Frosches."
     Archiv f. mikroskop Anat., 1869, V, 49-89.

100. GROSSER (O.). " Ueber arterio-venöse Anastomosen an den Extremitä-   273.
        tenenden beim Menschen und den krallentragenden Säugethieren."
     Archiv f. mikrosk. Anat. u. Entwickl., 1902, LX, 191-216.

101. HABERLANDT (G.). " Zur Anatomie und Physiologie der pflanzlichen   63.
        Brennhaare."
     Sitzungb. d. k. Akad. d. Wissens., Wien, mat. nat. cl., 1886, XCIII,
        Abth. I, 123-145.

102. HAGEN (W.). " Die Schwankungen im Capillarkreislauf. Ein Beitrag zu   197, 199.
        seiner Physiologie und Pathologie."
     Zeitschr. f. ges. exper. Med., 1921, XIV, 364-405.

103. HAGEN (W.). " Periodische, konstitutionelle und pathologische   199.
        Schwankungen im Verhalten der Blutcapillaren."
     Archiv f. pathol. Anat. u. Physiol., 1922, CCXXXIX, 504-556.

104. HAMMER. " Ueber den Einfluss des Lichtes auf die Haut."   118, 119.
     Stuttgart, 1891 (citation).

PAGE

105. HARE (R.). "An experimental investigation into the vascular reactions   113, 116, 240,
  of the susceptible skin to protein."   242, 244.
  Heart, 1926, XIII, 227-238.

106. HARMER (I. M.) and HARRIS (K.E.). "Observations on the vascular   104, 109, 236,
  reactions in man in response to histamine."   258.
  Heart, 1926, XIII, 381-394.

107. HARRIS (K. E.) and MARVIN (H. M.). (In the press.)   222.
  Heart, 1927, XIV.

108. HAUSMANN (W.). "Grundzüge der Lichtbiologie und Lichtpathologie."   129.
  Reprinted from " Strahlentherapie."
  Berlin and Vienna, 1923.

109. HAUSSER (K. W.) and VAHLE (W.).   118.
  Strahlentherapie, 1921, XIII, 41 (citation).

110. HEAD (H.). "Herpes zoster." In Allbutt and Rolleston's System of   213.
  Medicine, London, 1910, VII, 470.

111. HEAD (H.) and CAMPBELL (A. W.). "The pathology of herpes zoster   213.
  and its bearing on sensory localisation."
  Brain, 1900, XXIII, 353-523.

112. HEAD (H.) and SHERREN (J.). "The consequences of injury to the   214.
  peripheral nerves of man."
  Brain, 1905, XXVIII, 116-338.

112a. HEIMBERGER (H.). "Beiträge zur Physiologie der menschlichen   3, 32, 273.
  Capillaren."
  Zeitschr. f. d. ges. exper. Med., 1925, XLVI, 519-557.

112b. HEIMBERGER (H.). "Beiträge zur Physiologie der menschlichen   229.
  Capillaren. II. Mitt. Verhalten auf stumpfen mechanischen Reiz."
  Zeitschr. f. d. ges. exper. Med., 1926, XLIX, 411-429.

113. HELLWIG (A.). "Periarterielle Sympathektomie an der Carotid bei   210.
  Migräne."
  Archiv f. klin. Chirurg., 1924, CXXVIII, 261-285.

114. HERZ (M.). "Der Puls der kleinsten Gefässe."   267.
  Wiener Klinik, 1896, XXII, 165-212.

115. HEUBNER (W.). "Zur Pharmakologie der Reizstoffe."   137.
  Archiv f. exper. Pathol. u. Pharmakol., 1925, CVII, 129-154.

116. HEWLETT (A. W.) and ZWALUWENBURG (J. G. Van). "The rate of   73, 160.
  blood flow in the arm."
  Heart, 1909-10, I, 87-97.

117. HODARA (M.). "Untersuchungen über die Histologie der Urticaria   57.
  factitia (Dermatographismus)," etc.
  Dermatol. Wochenschr., 1913, LVII, 971-980.

118. HOGBEN (L. H.) and WINTON (F. R.) Studies on the pituitary. I. The   237.
  melanophore stimulant in posterior lobe extracts."
  Biochem. Journ. 1922, XVI, 619-630.

119. HOOKER (D. R.). "The effect of exercise upon the venous blood   34.
  pressure."
  Amer. Journ. of Physiol., 1911, XXVIII, 235-248.

120. HOOKER (D. R.). "The functional activity of the capillaries and   222.
  venules."
  Amer. Journ. of Physiol., 1920, LIV, 30-54.

121. HOYER (H.). "Ueber unmittelbare Einmündung kleinster Arterien in   2, 273.
  Gefässäste venösen Charakters."
  Archiv f. mikrosk. Anat., 1877, XIII, 603-650.

122. INCHLEY (O.). "Histamine shock."   109.
  Journ. of Physiol., 1926, LXI, 282-293.

123. JENDRASSIK (E.). "Einiges über Suggestion."   214.
  Neurolog. Centralbl., 1888, VII, 281 and 321.

PAGE

124. JÜRGENSEN (E.). "Mikrokapillarbeobachtungen und Puls der kleinsten   272.
    Gefässe."
    Zeitschr. f. klin. Med., 1918, LXXXVI, 410-434.

125. JÜRGENSEN (E.). "Mikrokapillarbeobachtungen. Ein Beitrag zur   272.
    pathologischen Physiologie des Kreislaufssystems."
    Deutsch. Archiv f. klin. Med., 1920, CXXXII, 204-218.

126. KALINDERO.   92.
    Congr. internat. d. Dermatol. e. d. Syph., Paris, 1889, 606-7.

127. KATZENSTEIN (M.). Über Entstehung und Wesen des arteriellen   152.
    Collateralkreislaufs."
    Deutsch. Zeitschr. f. Chirurg, 1905, LXXVII, 189-226.

128. KEITH (N. M.). " Blood volume in wound shock."   110.
    Medical research Committee Rep., London, 1919, No. 26, 36-44.

129. KENDREW (A.). " The graphic registration of venous pressure in man,   25, 173, 175.
    illustrated by some observations on reactive hyperæmia."
    Heart, 1926, XIII, 101-108.

130. KOHLER (R.) and WETH (G.). "Die Wirkung der cervicalen   207, 209, 210,
    Sympathektomie auf die Angina pectoris und die Ausfallerschein-   217.
    ungen nach diesem operativen Eingriff."
    Zeitschr. f. klin. Med., 1924, XCIX, 205-231.

131. KOHNSTAMM (O.). " Ueber hypnotische Behandlung," etc..   215.
    Therapie der Gegenwart, 1907, XLVIII, 354-359.

132. KRAFT-EBING (R.). "An experimental study in the domain of   214.
    hypnotism."...
    (Transl. by Chaddock), New York and London, 1889.

133. KRAUS (F.). "Erfahrungen über die intracranielle Trigeminusresec-   208.
    tion."
    Archiv f. klin. Chirurg., 1895, L, 469-494.

134. KROGH (A.). "The supply of oxygen to the tissues and the regulation   179, 199.
    of the capillary circulation."
    Journ. of Physiol., 1918-19, LII, 457-474.

135. KROGH (A.). "Studies on the capillariomotor mechanism. I. The   35, 222.
    reaction to stimuli and the innervation of the blood vessels in the
    tongue of the frog."
    Journ. of Physiol., 1919-20, LIII, 399-419.

136. KROGH (A.). "Studies on the physiology of capillaries. II. The reactions   35, 231.
    to local stimuli of the blood vessels in the skin and web of the frog."
    Journ. of Physiol., 1921, LV, 412-422.

137. KROGH (A.). "The Anatomy and Physiology of Capillaries."   24, 67, 152, 172,
    New Haven, 1922.   179, 188, 199,
    208, 231, 237,
    [279.

138. KROGH (A.). "The pituitary (posterior lobe) principle in circulating   237.
    blood."
    Journ. of Pharmacol. and exper. Therap., 1926, XXIX, 177-189.

139. KROGH (A.) HARROP (G. A.) and REHBERG (P. B.). "Studies on the   222.
    physiology of capillaries. III. The innervation of the blood vessels
    in the hind legs of the frog."
    Journ. of Physiol., 1922, LVI, 179-189.

140. KROGH (A.) and REHBERG (P. B.). " Sur l'influence de l'hypophyse sur   237.
    la tonicité des capillairies."
    Compt. rend. hebdo. d. l. Soc. d. Biol., 1922, LXXXVII, 461-63.

141. LANGLEY (J. N.). "Further observations on the secretory and vaso-   208.
    motor fibres of the foot of the cat, with notes on other sympathetic
    nerve fibres."
    Journ. of Physiol., 1894-5, XVII, 296-314.

142. LANGLEY (J. N.). "On axon reflexes in the preganglionic fibres of the   217.
    sympathetic nervous system."
    Journ. of Physiol., 1899-1900, XXV, 364-398.

PAGE

143. LANGLEY (J. N.). "Antidromic action. Part I."   210, 222.
　　　Journ. of Physiol., 1922-23, LVII, 428-446.

144. LANGLEY (J. N.). "Antidromic action. Part II. Stimulation of the   210, 211, 222.
　　　peripheral nerves of the cat's hind foot."
　　　Journ. of Physiol., 1923-24, LVIII, 49-69.

145. LANGLEY (J. N.). "The vascular dilatation caused by the sympathetic   210.
　　　and the course of vasomotor nerves."
　　　Journ. of Physiol., 1923-24, LVIII, 70-73.

146. LANGLEY (J. N.) and ANDERSON (H. K.). "On reflex action from   217.
　　　sympathetic ganglia."
　　　Journ. of Physiol., 1894, XVI, 410-440.

147. LAPINSKY (M.). "Uber den Mechanismus und die diagnostische   24.
　　　Bedeutung der Dermatographie am oberen Teile des Rückens und
　　　am hinteren Teile des Halses."
　　　Zeitschr. f. d. ges. Neurol. u. Psych., 1914, XXII, 58-96.

148. LEE (F. C.). "A note on differences of capillary activity."   108.
　　　Amer. Journ. of Physiol., 1925, LXXIV, 326-333.

149. LEHMAN (E. P.). "Periarterial sympathectomy."   210.
　　　Annals of Surgery, 1923, LXXVII, 30-37.

150. LEHMANN (W.). "Uber eigenartige Beziehungen zwischen der Ober-   210.
　　　flächen und Tiefensensibilität."
　　　Archiv f. Psychiat. u. Nervenkr., 1924, LXX, 309-316.

151. LEHNER (E.) and KENEDY (D.). "Zur Kenntnis der Entzündungen der   197, 261, 292.
　　　Haut mit netzförmiger oder verästelter Zeichnung."
　　　Archiv f. Dermatol. u. Syph., 1922, CXLI, 325-341.

152. LEHNER (E.) and KENEDY (D.). "Weitere Beiträge zur Kenntnis   197, 261, 292.
　　　der Entzündungen der Haut mit netzförmiger oder verästelter
　　　Zeichnung. Inflammatio cutis racemosa."
　　　Archiv f. Dermatol. u. Syph., 1925, CXLIX, 387-392.

153. LEHNER (E.) and RAJKA (E.). "Gelungener uebertragungsversuch   116.
　　　einer experimentell hervorgerufenen Senfölüberempfindlichkeit."
　　　Deutsch. med. Wochenschr., 1925, LI, 825.

154. LERICHE (R.). "De l'élongation et de la section des nerfs périvasculaires,"   210.
　　　etc. Lyon Chirurg., 1913, X, 378.
　　　See also Leriche and Heitz, Compt. rend. hebdo. d. l. Soc. d. Biol.,
　　　1917, LXXX, 66-70 and 160-162.

155. LERICHE (R.) and POLICARD (R.). "Étude de la circulation capillaire   221.
　　　chez l'homme pendant l'excitation des nerfs sympathiques
　　　périartériels et la ligature des artères."
　　　Lyon Chirurg., 1920, XVII, 703-704.

156. LEVINE (S. A.) and NEWTON (F. C.). "The selection of patients with   207.
　　　angina pectoris for sympathectomy ; with a report of additional
　　　cases."
　　　Amer. heart Journ., 1925, I, 41-61.

157. LEWIS (T.). "The force exerted by contracted capillaries."   24, 31, 32, 34.
　　　Journ. of Physiol., 1923, LVIII, Proc. I, Oct. 20th, 1923.

158. LEWIS (T.). "The force exerted by the minute vessels of the skin in   20, 24, 32, 34.
　　　contracting."
　　　Heart, 1924, XI, 109-118.

159. LEWIS (T.). "Vascular reactions of the skin to injury. Part I. Reaction   46, 73, 74, 75,
　　　to stroking ; urticaria factitia."   79.
　　　Heart, 1924, XI, 119-140.

160. LEWIS (T.). "Studies of capillary pulsation, with special reference to   2, 11, 141, 142,
　　　vasodilatation in aortic regurgitation and including observations on   143, 226, 227,
　　　the effects of heating the human skin."   228, 267, 268,
　　　Heart. 1924, XI, 151-194.   269, 271, 273.

161. LEWIS (T.). "Observations upon the regulation of blood flow through   44, 189, 197,
　　　the capillaries of the human skin."   198, 260.
　　　Heart, 1926, XIII, 1-26.

PAGE

162. Lewis (T.). " Vascular reactions of the skin to injury. Part IV. An irresponsive condition of the vessels with special reference to the pathology of telangiectases and allied conditions."
Heart, 1926, xiii, 153-192.

202, 240, 255, 256, 261, 290, 292.

163. Lewis (T.) and Drury (A. N.). " Observations relating to arterio-venous aneurism. Part I. Circulatory manifestations in clinical cases with particular reference to the arterial phenomena of aortic regurgitation."
Heart, 1923, x, 301-364.

227, 267.

164. Lewis (T.) and Grant (R. T.). " Vascular reactions of the skin to injury. Part II. The liberation of a histamine-like substance in injured skin ; the underlying cause of factitious urticaria and of wheals produced by burning ; and observations upon the nervous control of certain skin reactions."
Heart, 1924, xi, 209-265.

18, 41, 56, 59, 64, 68, 69, 70, 72, 79, 82 to 85, 88, 89, 92, 93, 95, 96, 97, 99, 101, 103, 149, 151, 186, 209, 237, 244.

165. Lewis (T.) and Grant (R. T.). " Observations upon reactive hyperæmia in man."
Heart, 1925-26, xii, 73-120.

32, 141, 152, 153, 158, 162, 165, 167, 168, 169, 171, 172, 174, 182, 233.

166. Lewis (T.) and Grant (R. T.). " Vascular reactions of the skin to injury. Part VII. Notes on the anaphylactic skin reaction."
Heart, 1926, xiii, 219-225.

113.

167. Lewis (T.) and Grant (R. T.) and Harris (K. E.). " Observations relating to the influence of the cutaneous nerves on various reactions of the cutaneous vessels."
Heart, 1927, xiv, 1-17.

31, 32, 68, 69, 70, 72, 119, 135, 144, 203, 209, 216, 244, 260.

168. Lewis (T.) and Harmer (I. M.). " Observations upon the rupture of minute vessels in the skin and upon the distribution of cutaneous hæmorrhages and other skin eruptions."
Heart, 1926, xiii, 337-355.

290, 292, 293.

169. Lewis (T.) and Harmer (I. M.). " Release of vaso-dilator substances in injuries of the skin."
Journ. of Physiol., 1926-27, lxii, Proc. xi, Oct. 16th, 1926.

104, 111.

170. Lewis (T.) and Harmer (I. M.). " Vascular reactions of the skin to injury. Part IX. Further evidence of the release of a histamine-like substance from the injured skin."
Heart, 1927, xiv, 19-26.

104, 111, 236, 258.

171. Lewis (T.) and Love (W. S.). " Vascular reactions of the skin to injury. Part III. Some effects of freezing, of cooling and of warming."
Heart, 1926, xiii, 27-60.

51, 54, 55, 57, 89, 141, 143, 144, 145, 147, 148, 149.

172. Lewis (T.) and Marvin (H. M.). " Herpes zoster and antidromic impulses."
Journ. of Physiol., 1926-27, lxii, Proc. xix, Nov. 13th, 1926.

109, 211, 222.

173. Lewis (T.) and Marvin (H. M.) " Observations relating to vaso-dilatation arising from antidromic impulses, to herpes zoster and trophic effects."
Heart, 1927, xiv, 27-48.

209, 211, 222.

174. Lewis (T.) and Zotterman (Y.). " Vascular reactions of the skin to injury. Part V. Annular œdema of the skin in a case of infective endocarditis."
Heart, 1926, xiii, 193-202.

247, 292.

175. Lewis (T.) and Zotterman (Y.). " Vascular reactions of the skin to injury. Part VI. Some effects of ultra-violet light."
Heart, 1926, xiii, 203-218.

118, 119, 128.

PAGE

176. LEWIS (T.) and ZOTTERMAN (Y.). " Vascular reactions of the skin to   58, 83.
          injury. Part VIII. The resistance of the human skin to constant
          currents, in relation to injury and vascular response."
          Journ. of Physiol., 1926-27, LXII, 280-88.

177. LISTER (J.). " On the early stages of inflammation."   231.
          Phil. Trans. Roy. Soc., 1858, CXLVIII, 645-702.

178. LISTER. " De l'influence de la position des membres sur la circulation."   151.
          Bull. d. l'Acad. d. Med. (Paris), 1878, 2nd Lec., VII, 640-643.

179. LOMBARD (W. P.). " The blood pressure in the arterioles, and small   7.
          veins of the human skin."
          Amer. Journ. of Physiol., 1911-12, XXIX, 335-362.

180. LOVÉN (C.). " Über die Erweiterung von Arterien in Folge einer   67, 207.
          Nervenerregung."
          Berichte. u. d. Verhandl. d. könig. sächs. Gessels. d. wissens. z.
          Leipzig, 1866, XVIII (math.-phys. Cl.) 85 110.

181. LOW (C.). " Carbonic-acid snow as a therapeutic agent in the treatment   54.
          of diseases of the skin."
          Edinb. and London, 1911.

182. LOW (C. R.). " Anaphylaxis and Sensitisation."   116.
          Edinb., 1924.

183. MACKENZIE (J.). " A new outlook in cardiology."   188.
          Brit. med. Journ., 1924, I, 104-109.

184. MANN (F. C.). " Shock and hæmorrhage : an experimental study."   110.
          Surg. Gynæc. and Obstet., 1915, XXI, 430-439.

185. MANN (F. C.). " Studies on experimental surgical shock."   110.
          Amer. Journ. of Physiol., 1918-19, XLVII, 231-249.

185a. MARCHAND (F.). " Ueber die Kontraktilität der Kapillaren und die   35.
          Adventitialzellen."
          München. med. Wochenschr., 1923, LXX, 385-387.

186. MARKWALDER (J.) and STARLING (E. H.). " A note on some factors   187.
          which determine the blood-flow through the coronary circulation."
          Journ. of Physiol., 1913-14, XLVII, 275-285.

187. MAYER (S.). " Die Muscularisirung der capillaren Blutgefässe."   35.
          Anat. Anz., 1902, XXI, 442-455.

188. MAYER-BETZ (F.). " Untersuchungen über die biologische (photo-   129.
          dynamische) Wirkung der Hämatoporphyrins," etc.
          Deutsch Archiv f. klin. Med., 1913, CXII, 476-503.

189. MEAKINS (J.) and DAVIES (H. W.). " Observations on the gases in   146.
          human arterial and venous blood."
          Journ. of Pathol. and Bacteriol., 1919-20, XXIII, 451-461.

190. MICHIELS (J.) and SCHICK (B.). " Die Intracutan-reaktion des Menschen   133.
          auf Diphtherietoxininjection als Ausdruck des Schutzkörpergehaltes
          seines Serums."
          Zeitschr. f. Kinderheilk., 1913, V, 255-259.

191. MITCHELL (S. WEIR). " Injuries of Nerves and their Consequences."   214.
          Philadelphia, 1872, pages 148, and 153 to 157 especially.

192. MÖLLER (M.). " Der Einfluss des Lichtes auf die Haut in gesunden   256.
          und krankhaften Zustande."
          Bibliotheca Medica. Abth. D II, Hft 8. " Dermatologie und Syphili-
          dologie," Stuttgart, 1900.

193. MOLL (A.) " Hypnotism." Contemporary science series.   215.
          London, 1890, 2nd Ed., p. 119.

194. MORTON (H. H. P.). " A case of herpes zoster, apparently due to   213.
          invasion of the ganglia by round-cell sarcoma."
          Journ. of Neurol. and Psychopathol., 1926, VI, 296-300.

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195. MOYCHO (V.). "Étude physiologique de l'action des rayons ultra-   118.
violets sur l'oreille de lapin."
Comp. rend. hebdo. d. l. Soc. d. Biol., 1913, LXXV, 192-194.

196. MÜLLER (L. R.). "Studien über den Dermographismus und dessen   23, 24, 37, 42,
diagnostische Bedeutung."   46, 67, 68, 69.
Deutsch. Zeitschr. f. Nervenheilk., 1913, XLVII-VIII, 413-435.

197. MÜLLER (O.). "Die Kapillaren der menschlichen Körperoberfläche in   7.
gesunden und kranken Tagen."
Stuttgart, 1922.

198. NATUS (M.). "Beiträge zur Lehre von der Stase nach Versuchen am   142.
Pankreas des lebenden Kaninchen."
Archiv f. pathol. Anat. u. Physiol., 1910, CXCIX, 1-82.

199. NEUMANN (R.). "Kapillarstudien mittels der mikroskopischen   25, 197.
Kapillarbeobachtungsmethode nach Müller-Weiss. i Mitt. Die
Strömung in den Kapillaren."
Berl. klin. Wochenschr., 1920, LVII, 826-829.

200. OCHS (B. F.). "A case of urticaria caused by the sun's rays."   129.
Med. Record, 1910, LXXVIII, 193.

201. OSLER (W.). "On multiple hereditary telangiectases with recurring
hæmorrhages."
Quart. Journ. of Med., 1907-8, I, 53-58.

202. PAGET. "Some cases of local paralysis."   214.
Med. Times and Gaz., 1864, I, 331-332.

203. PARRISIUS (W.). "Kapillarstudien bei Vasoneurosen."   29, 72.
Deutsch. Zeitschr. f. Nervenheilk., 1921, LXXII, 310-358.

204. PHILLIPSON (L.). "Richerche sperimentali sull' urticaria." Giorn.   63.
Ital. malen. e. mal. pele, 1899 (see abstract in Archiv f. Dermatol.
u. Syph., 1900, LI, 48).

205. PIRQUET (C. F.). "Das Bild der Masern auf der äusseren Haut."   393.
Zeitschr. f. Kinderheilk., 1913, VI, 1-226.

206. POHLE (E.). "Der Einfluss des Nervensystems auf die Osmoregulation   237.
der Amphibien."
Archiv f. d. ges. Physiol., 1920, CLXXXII, 215-231.

207. QUÉNU (E.). Bull. e. Mém. d. l. Soc. d. Chirurg., 1917, XLIII, 2169-2179   110.
(see also page 2122).

208. QUÉNU. Compt. rend. hebdo. d. l. Soc. d. Biol., Paris, 1918, LXXXI, 858.   110.

209. QUINCKE (H.). "Beobachtungen über Capillar-und Venenpuls."   266, 268.
Berl. klin. Wochenschr., 1868, V, 357-359.

210. QUINCKE (H.). "Ueber Capillarpuls und centripetal Venenpuls."   273.
Berl. klin. Wochenschr., 1890, XXVII, 265-267.

211. RAJKA (E.). "Uber das Verhalten der Haut nach quaddelerzeugenden   73, 93.
Einwirkungen bei vollständiger Unterbrechung des Blutkreislaufs."
Archiv f. Dermatol. u. Syph., 1925, CXLIX, 525-533.

212. RAJKA (E.). and FÜRTH (J.). "Ueber die Genese der reflektorischen   67.
Umgebungshyperämie unter physiologischen und pathologischen
Verhältnissen."
Deutsch. med. Wochenschr., 1924, L, 1575-1576.

213. RECKLINGHAUSEN (H. v.). "Unblutige Blutmessung III. Messung des   34.
Blutdrucks in den kleinen Arterien, Venen und Kapillaren des
Menschen und beim Tier."
Archiv f. exper. Pathol. u. Pharmakol., 1906, LV, 463-504.

PAGE

214. REHBERG (P. B.) and CARRIER (E. B.). "Studies on the physiology of   42, 152, 220,
     capillaries. V. Concerning the reaction of the human skin   275, 279, 281.
     capillaries to venous blood."
     Skand. Archiv f. Physiol., 1922, XLII, 250-265.

215. RENAUT (J.). "Dermatoses" in Dictionnaire encyclop. d. Sc. med.,   260.
     Paris, 1883, XXVIII, p. 158, etc.

216. RENAUT. "Sur une forme de la gangrène successive et disseminé de   47.
     la peau : l'urticaire gangréneuse."
     Médicine moderne, 1890, I, 163.

217. RICHARDS (A. N.) and SCHMIDT (C. F.). "A description of the   199.
     glomerular circulation in the frog's kidney and observations
     concerning the action of adrenalin and various other substances
     upon it."
     Amer. Journ. of Physiol., 1924, LXXI, 178-208. (See also Amer. Journ.
     med. Sci., 1922, CLXIII, 1-19.)

218. RICKER (G.) and REGENDANZ (P.). "Beiträge zur Kenntnis der   142.
     örtlichen Krieslaufsstörungen," etc.
     Archiv f. patholog. Anat. u. Physiol., 1921, CCXXXI, 1-184.

219. ROBERTSON (B.) and BOYD (G. L.). "The toxæmia of severe superficial   111.
     burns."
     Journ. of lab. and clin. Med., 1923-24, IX, 1-14.

220. ROUGET (C.). "Note sur le développement de la tunique contractile   34, 35.
     des vaisseaux."
     Compt. rend. hebdo. d. l'Acad. d. Sc., 1874, LXXIX, 559-562.

221. ROUGET (C.). "Sur la contractilité des capillaires sanguins."   34, 35.
     Compt. rend. hebdo. d. l'Acad. d. Sc., 1879, LXXXVIII, 916-918.

222. ROY (C. S.) and BROWN (J. G.). "The blood pressure and its variations   35, 169, 172,
     in the arterioles, capillaries and small veins."   181, 187.
     Journ. of Physiol., 1879-80, II, 323-359.

223. SACKS (B.). "Observations upon the vascular reactions in man in   32, 179, 237.
     response to infundin, with special reference to the behaviour of the
     capillaries and venules."
     Heart, 1924, XI, 353-370.

223a. SCHENK (P.). "Uber die Wirkungsweise des B-imidazolyläthylamins   109.
     (Histamin) auf den menschlichen Organismus."
     Archiv f. exper. Pathol. u. Pharmakol., 1921, LXXXIX, 332-39.

224. SCHILF (E.). "Physiologische Versuche zur periarteriellen Sympa-   210.
     thektomie."
     Klin. Wochenschr., 1924, III, 346.

225. SCHWARZ (C.) and LEMBERGER (F.). "Uber die Wirkungkleinster   179.
     Säuremengen auf die Blutgefässe."
     Archiv f. d. ges. Physiol., 1911, CXLI, 149-170.

226. SEVERINI. "La contrattilit dei vasa capillari in relazione ai due gas   179.
     dello scambio materiale."
     Perugia, 1881 (Citation).

227. SHERRINGTON (C. S.) and COPEMAN (S. M.). "Variations experimentally   110.
     produced in the specific gravity of the blood."
     Journ. of Physiol., 1893, XIV, 52-96.

228. SOBOTKA (P.). "Studien über den Einfluss experimentell veränderter   119.
     örtlicher Bedingungen auf die Lichtreaktion (Ultraviolettreaktion)
     der menschlichen Haut."
     Archiv f. Dermatol. u. Syph., 1915-16, CXXI, 45-159.

229. SOLLMANN (T.) and PILCHER (J. D.). "Endermic reactions."   59, 63, 103.
     Journ. of Pharmacol. and exper. Therap., 1917, IX, 309-340.

230. SOLTAU (A. B.). "Vesicants. Mustard gas." in History of the Great   134.
     War (Med. Serv.), London, 1923, II, 425-462.

PAGE

231. SPALTEHOLZ (W.). " Die Vertheilung der Blutgefässe in der Haut."   1, 2, 43, 109,
      Archiv f. Anat. u. Physiol., 1893 (Anat. Abth.), 1-54.   204, 249.

231a. SPALTEHOLZ (W.). " Blutgefässe der Haut." Handb. d. Haut u.   1, 2, 29, 35,
      Geschlechtskr. 1927, Bd, i, Th. i, 379-433.   109, 274.

232. STARLING (E. H.). " The production and absorption of lymph."   79.
      Schäfer's " Text-book of Physiology." 1898, I, p. 296 and Lancet,
      1896, I, 1267.

233. STEINACH (E.) and KAHN (R. H.). " Echte Contractilität und   35, 221.
      motorische Innervation der Blutcapillaren."
      Archiv f. d. ges. Physiol., 1903, XCVII, 105-133.

234. STEWART (G. N.). " Studies on the circulation in man. I. The measure-   73.
      ment of the blood flow in the hands."
      Heart, 1911-12, III, 33-75.

235. STEWART (G. N.). " Studies on the circulation in man. II. The effect   142.
      of reflex vaso-motor excitation on the blood flow in the hand."
      Heart, 1911-12, III, 76-88.

236. STEWART (G. N.). " Studies on the circulation in man. V. Effect on   74.
      the blood flow in the hand of applying different pressures on the
      upper arm," etc..
      Archives of internal Med., 1912, LX, 706-735.

236a. STÖHR (P.). " Mikroskopischer Beitrag zur Innervation der Blut-   221.
      capillaren beim Menschen."
      Zeitschr. f. Zellforsch. u. mikrosk. Anat., 1926, III, 431-448.

237. STRAUB (W.). " Zur chemischen Kinetik der Muskarinwirkung und des   244.
      Antagonismus Muskarin-Atropin."
      Archiv f. d. ges. Physiol., 1907, CXIX, 127-151.

238. STRICKER (S.). " Studien über den Bau und das Leben der capillaren   34.
      Blutgefässe."
      Sitzungsb. d. k. Akad. d. Wissens., Wien, math. nat. Cl., 1865, LII,
      Abth. II, 379-394.

239. STRICKER (S.). " Untersuchungen über die capillaren Blutgefässe in der   34.
      Nickhaut des Frosches."
      Sitzungsb. d. k. Akad. d. Wissens., Wien, math. nat. Cl., 1865, LI,
      Abth. II, 16-27.

240. STRICKER (S.). " Untersuchungen über die Gefässnerven-Wurzeln des   210.
      Ischiadicus."
      Sitzungsb. d. k. Akad. d. Wissens., Wien, math. nat. Cl., 1876, LXXIV,
      Abth. III, 173-185.

241. STRICKER (S.). " Untersuchungen über die Contractilität der   34.
      Capillaren."
      Sitzungsb. d. k. Akad. d. Wissens, Wien, math. nat. Cl.,1876, LXXIV,
      Abth, III, 313-332.

242. SUCQUET (J. P.). " D'une Circulation derivative dans les Membres et   273.
      dans la Tête chez l'Homme."
      Paris, 1862.

243. SUMBAL. (J. J.). " The vessels concerned in clinical capillary pulsation."   272.
      Heart, 1923, X, 271-74.

243a. TANNENBERG (J.). " Bau und Function der Blutkapillaren."   35.
      Frankf. Zeitschr. f. Pathol., 1926, XXXIV, 1-19.

244. TARCHANOFF (J. F.). " Beobachtungen über contractile Elemente in   34.
      den Blut-und Lymphcapillaren."
      Archiv f. d. ges. Physiol., 1874, IX, 407-416.

245. TOMITA (C.). " Ueber die Hyperämie der Haut nach v. Esmarch'scher   153.
      Blutleere."
      Archiv f. d. ges. Physiol., 1907, CXVI, 299-306.

PAGE

246. TÖRÖK (L.). "Ueber das Wesen der sogenannten Angioneurosen der　79.
Haut," etc.
Archiv f. Dermatol. u. Syph., 1900, LIII, 243-268.

247. TÖRÖK (L.) and HARI (P.). "Experimentelle Untersuchungen über die　63.
Pathogenese der Urticaria."
Archiv f. Dermatol. u. Syph., 1903, LXV, 21-36.

248. TÖRÖK (L.), LEHNER (E.) and URBÁN (F.). "Über Veränderungen der　116, 245.
Reaktion der Haut nach wiederholten Einwirkung auf dieselbe
Hautstelle."
Kranheitsforschung, 1925, I, Hft. 5, 371-406.

249. TÖRÖK (L.) and RAJKA (E.). "Beitrag zur Pathogenese der Hyper-　69, 73.
ämie und des Ödems bei der Urticaria und der akuten Entzündung
der Haut."
Archiv f. Dermatol. u. Syph., 1924, CXLVII, 559-580.

250. TÖRÖK (L.) and RAJKA (E.). "Über den Einfluss der kongestiven　92, 93, 99, 186.
Hyperämie und der Stauung auf die Quaddelbildung."
Dermatol. Wochenschr., 1925, LXXXI, 1031-1040.

251. TÖRÖK (L.) and RAJKA (E.). "Experimentelle Untersuchungen über　69.
die Entstehung des hyperämischen Entzündungshofes."
Wien. med. Wochenschr., 1925, LXXV, 383-386.

252. TROTTER (W.) and DAVIES (H. M.). "Experimental studies in the　69, 208.
innervation of the skin."
Journ. of Physiol., 1909, XXXVIII, 134-246 (pages 172 and 188).

253. UNDERHILL (F. P.) and PACK (G. T.). "Blood concentration changes　111.
in extensive superficial burns, and their significance for systematic
treatment."
Archives of internal Med., 1923, XXXII, 31-49.

254. VERNEY (E. B.). "The secretion of pituitrin in mammals, as shown　237.
by perfusing the isolated kidney of the dog."
Proc. Roy. Soc., 1926, B. XCIX, 487-517.

255. VIMTRUP (B.). "Beiträge zur Anatomie der Capillaren. I. Über con-　35.
tractile Elemente in der Gefässwand der Blutcapillaren."
Zeitschr. f. Anat. u. Entwickl., 1922, LV, 150-182.

256. VIMTRUP (Bj.). "Beiträge zur Anatomie der Capillaren. II. Weitere　2, 29, 35.
Untersuchungen über contractile Elemente in der Gefässwande
der Blutcapillaren."
Zeitschr. f. Anat. u. Entwickl., 1923, LXVIII, 469-482.

257. VOLKMANN (R.). "Handbuch d. allg. u. spec. Chirurgie (Pitha and　157.
Billroth)."
Stuttgart, 1882, II, Abth. 2, Absch. v, Erste Hälfte. Footnote p. 846.

258. WALL (R. C. B.) and WALKER (E. W. A.). "An explanation of the cause　207.
of inequality of pu ils in cases of thoracic aneurysm."
Lancet, 1902, II, 68-72.

259. WARD (S. B.). "Erythema and urticaria, with a condition resembling　129.
angeioneurotic œdema, caused only by exposure to the sun's rays."
New York med. Journ., 1905, LXXXI, 742-43.

260. WARTHIN (A. S.) and WELLER (C. V.). "The medical Aspects of Mustard　134.
Gas Poisoning," London, 1919.

261. WEISS (E.). "Beobachtung und mikrophotographishe Darstellun　7.
der Hautkapillaren am lebenden Menschen."
Deutsch. Archiv f. klin. Med., 1916, CXIX, 1-38.

262. WEISS (E.) and HOLLAND (M.). "Zur Morphologie und Topographie　7.
der Hautkapillaren."
Zeitschr. f. exper. Pathol. u. Therap., 1921, XXII, 108-134.

263. WETZEL (N. C.) and ZOTTERMAN (Y.). "On differences in the vascular　17, 18, 249, 254,
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Heart, 1926, xiii, 358-370.

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264. WIDMARK (E. J.). "Ueber den Einfluss des Lichtes auf die vorderen   117.
    Medien des Auges."
    Skand. Archiv f. Physiol., 1889, I, 264-330.

265. WIEDHOFF (O.). Experimentelle Untersuchungen über die Wirkung   210.
    der periarteriellen Sympathectomie und der Nervenreizung auf
    die Gefässe der Extremitäten."
    Beitr. z. klin. Chirurg., 1924, CXXX, 399-445.

266. WILLIS (A. M.). "The value of débridement in the treatment of burns."   111.
    Journ. Amer. med. Assoc., 1925, LXXXIV, 655-658.

267. WOLF (E. P.). "Experimental studies on inflammation. I. The in-   106.
    fluence of chemicals upon the chemotaxis of leucocytes in vitro."
    Journ. exper. Med., 1921, XXXIV, 375-396.

268. WOLF (E. P.). "Experimental studies on inflammation. II. Experi-   106.
    mental chemical inflammation in vivo."
    Journ. exper. Med., 1923, XXXVII, 511-524.

269. WOLF (E. P.). "Local changes of colour in the skin deprived of its   275, 279, 281.
    normal blood supply; with remarks on local asphyxia."
    Heart, 1924, XI, 327-335.

270. WOOLLARD (H. H.). "The innervation of blood vessels."   206, 211, 217,
    Heart, 1926, XIII, 319-336.   220, 221, 222.

271. ZAK (E.). "Uber den Gefässkrampf bei intermittierenden Hinken und   152, 279.
    über gewisse kapillomotorische Erscheinungen."
    Wien. Archiv f. inn. Med., 1921, II, 405-420.

272. ZIMMERMANN (K. W.). "Die feinere Bau der Blutcapillaren."   35.
    Zeitschr. f. Anat. u. Entwickl., 1923, LXVIII, 29-109.

273. ZINSSER (H.). "Infection and Resistance."   116.
    New York, 1923, 3rd Ed., chapters XVI to XVIII.

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